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ENTERIC INFECTIONS AND THEIR SEQUELAE*

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THE acute dysenteric diseases have been studied in various overseas installations throughout the world, but follow-up studies are scarce. Most of the patients in this group were carefully observed overseas, and in many cases the complete clinical record was available, making the follow-up study particularly significant. The cases referred to below were observed on the gastrointestinal section of a United States Army general hospital during the latter half of 1945. Attention was centered on the problems of diagnosis and treatment, since little importance could be attached to incidence in such a selected group of cases.

Overseas records and routine case histories were supplemented by systematic interviews that could be charted in tabular form. All the patients were allowed home for thirty to sixty days before final checkup, to provide a sufficiently long follow-up period after treatment, and practically all were examined with a sigmoidoscope. The laboratory study included at least six stool examinations, one specimen being obtained from sigmoid washings and one after purgation. Stool cultures were supplemented by rectal cultures. When steatorrhea was suspected a twenty-four-hour stool was collected for further observation.

An over-all picture of the cases studied is presented in Table 1, which lists the diagnoses made overseas and in the United States. Amebiasis was diagnosed in over a fourth of the cases. The number of patients diagnosed as carriers of *Endamoeba histolytica* was larger in the United States than overseas. The incidence of hookworm infestation was identical, with as many new cases as old ones that had been cleared of parasites. More patients were found to have strongyloidiasis in the United States than overseas. No new cases of schistosomiasis were discovered, and in several of the old cases negative stools were observed in the United States, where there was a marked increase in the number of diagnoses of such sequelae of intestinal disease as colitis, chronic diarrhea and steatorrhea.

Of the 105 men in this group, only 2 had never been overseas; 11 had served in the European Theater of Operations, and 92 had been in the Pacific, including the China and India-Burma theaters. Many of those from the Pacific had served in several areas, and a considerable number had no symptoms until they returned to the United States. Some patients had no symptoms of enteric disease and no pathological findings other than eosinophilia and ova in the stools. Such patients are referred to below as carriers. In Table 1 the infestations that were diagnosed in the United States are divided into active and carrier cases. With hookworm and ascaris infestation the number of carriers far exceeded those with symptoms. In amebiasis, strongyloidiasis and schistosomiasis there were more patients with symptoms than there were carriers. Patients with active cases were admitted to the ward for obvious reasons, whereas carriers were found through routine examination or because of stool studies ordered after eosinophilia had been noted.

TABLE 1. *Summary of Enteric Diseases.*

DISEASE	CASES DIAGNOSED OVERSEAS	CASES DIAGNOSED IN THE UNITED STATES		
		ACTIVE CASES	CARRIERS	TOTAL CASES
Ankylostomiasis	29	0	32	32
Amebic dysentery	37	28	15	43
Amebic hepatitis	3	2	0	2
Amebic liver abscess	5	2	0	2
Schistosomiasis	15	7	1	8
Strongyloidiasis	10	10	5	15
Ascariasis	6	1	4	5
Bacillary dysentery	5	0	1	1
Unclassified dysentery	9	1	0	1
Steatorrhea	2	7	0	7
Chronic diarrhea	0	11	0	11
Ulcerative colitis	2	4	0	4
Rectal granuloma	0	3	0	3
Mucous colitis	0	2	0	2
Rectal stricture	1	1	0	1
Appendiceal cyst	0	1	0	1
Totals	124	80	58	138

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In this group of patients the average duration of illness before arrival in the United States was six months, and the average length of hospital stay in the United States was three months. The latent period from exposure to illness varied from one to twenty-four months. Of the entire group of 105 men only a fourth were discharged from the section as fit for full duty.

Carriers of *Endamoeba Histolytica*

A carrier of *E. histolytica* is by definition a person who harbors the organism without having signs or symptoms of disease that might be associated with this infestation. It is well known that when the stool is solid the amebas are usually encysted and that when the stool is liquid for any reason the organisms are usually motile. Of the 15 patients diagnosed as carriers in the United States 64 per cent harbored cysts, 30 per cent harbored trophozoites and 6 per cent showed both cysts and trophozoites. Most of these patients were under investigation for some other disease, and amebas were found during routine stool examinations. In 1 case the organisms were discovered in a purged stool sent to the laboratory after administration of a vermifuge.

The final results in the 5 carrier cases of *E. histolytica* that were found overseas are summarized in Table 2. These men were not given antiamebic treatment overseas because of the presence of more serious disease. One man, nevertheless, remained symptom free, and amebas were not found in the stools. Another remained asymptomatic but was found to harbor cysts. Another remained asymptomatic but was found to harbor trophozoites. One patient developed diarrhea that subsided after antiamebic treatment. The last man developed typical amebic dysentery and was found to have trophozoites. Thus, in the 5 cases, 4 patients were eventually treated.

At first, carriers of *E. histolytica* were treated according to the conventional routine described below, Diodoquin being used instead of chiniofon because of the high incidence of diarrhea with the latter.[1] Nevertheless, 20 per cent of the carriers developed diarrhea with carbarsone. Subsequently carrier cases were treated with vioform alone.

Amebic Dysentery

In this group of men a diagnosis of amebic dysentery was made overseas in 30 cases and in the United States in 20. Most of the cases were contracted in or after exposure in the Pacific Theater. A few patients came from the China and India-Burma theaters, and a few from the European Theater, despite the disproportion in the number of troops exposed. There was a latent period of at least one to nine months from exposure until onset of the disease in the 20 cases diagnosed in the United States.

Although most of the patients with amebic dysentery were found to harbor trophozoites, cysts were discovered in a significant number (Table 3). In 3 cases the diagnosis was not established until a purged stool specimen was obtained, and in 2 the first positive specimen was obtained from sigmoid washings. Of the 20 cases in the United States complement-fixation tests were positive in only 7 (Table 4). Six cases were severe, 5 leading to ulceration and 1 being accompanied by hepatitis. In none of the 20 carrier cases diagnosed in the United States was the complement-fixation test positive. Con-

Table 2. *Final Results of Treatment in 5 Carrier Cases of* Endamoeba Histolytica *Diagnosed in the Pacific Theater and Followed in the United States.*

Case No.	History of Diarrhea	Other Disease	Findings Overseas	Treatment Overseas	Symptoms in United States	Findings in United States	Treatment in United States
1	Yes	Hepatitis	Cysts	None	None	None	None
2	Yes	Hepatitis and schistosomiasis	Cysts	Mapharsen and fuadin	None	Cysts	Carbarsone and Diodoquin
3	Yes	Schistosomiasis	Trophozoites	Sulfaguanidine and fuadin	None	Trophozoites	Carbarsone, Diodoquin and emetine
4	Yes	Schistosomiasis	Trophozoites	Fuadin	Diarrhea	Trophozoites	Carbarsone, Diodoquin and emetine
5	Yes	Hepatitis	Trophozoites	None	Diarrhea	None	Vioform

Table 3. *Severity of Attacks of Amebic Dysentery as Indicated by Associated Findings.*

Occurrence of Attack	Total No. of Patients*	Trophozoites	Cysts	Diarrhea	Watery Stools	Bloody Stools	Ulceration	Relapses	Other Complications	Drug Reactions
		%	%	%	%	%	%	%	%	%
Overseas	30	83	17	97	93	50	59	40	60	10
In the United States .	20	80	25	75	55	15	25	5	10	0

*Enemas were administered to 13 per cent of patients overseas and to 25 per cent of patients in the United States.

trary to the experience of others,[2] the test was of no value in picking up cases of intestinal amebiasis.

Attacks of amebic dysentery in persons returning from overseas were less severe than those occurring overseas but severer than similar infections acquired in the United States. The overseas attacks were almost invariably accompanied by severe diarrhea and the incidence of ulceration was high (Table 3). The overseas recurrence rate of over 40 per cent scess, 2 of appendicitis and 1 of mucous colitis. Of the patients who had amebic dysentery in the United States 1 was found to have granuloma and another developed chronic diarrhea. The disproportion in the number of complications in the two groups may have been due to several factors. In the first place, it was chiefly patients with complicated cases that were returned to the United States. Secondly, the overseas attacks were severer. Finally, thorough

TABLE 4. *Cases of Amebic Dysentery with Positive Complement-Fixation Tests.*

DATE OF POSITIVE STOOL EXAMINATION	DATE OF TREATMENT	DATE OF POSITIVE COMPLEMENT-FIXATION TEST	REMARKS AND COMPLICATIONS
April 20, 1945	April 30, 1945	—	Two attacks of dysentery, with rectal stricture
May 24, 1945	July 1, 1945	July 7, 1945	
September, 1944	September, 1945	—	Eight attacks of dysentery, with ulceration
July 22, 1945	August 1, 1945	July 7, 1945	
March 22, 1945	March 28, 1945	—	Two attacks of dysentery, with ulceration
August 3, 1945	August 16, 1945	August 7, 1945	
—	February 22, 1945	—	Probably 2 attacks of dysentery, with ulceration
May 31, 1945	August 16, 1945	July 31, 1945	
February 18, 1945	February 22, 1945	—	Ulceration and ulcerative colitis
—	June 20, 1945	July 31, 1945	
May 29, 1945	May 13, 1945	—	Amebic hepatitis and dysentery
June 23, 1945	June 8, 1945	August 7, 1945	
—	—	—	Chronic dysentery (since 1944), with ulceration
August 21, 1945	August 22, 1945	August 21, 1945	

contrasts with that of 5 per cent in the United States and may partly have been due to the fact that with one exception patients overseas were not given retention enemas in the treatment of the first attack (Table 3).

Most of the overseas attacks of amebic dysentery were treated with approximately a week of emetine, carbarsone and chiniofon. In Table 5 the treatment

treatment with retention enemas may have prevented some of the complications of amebic dysentery.

Diarrhea following the administration of chiniofon and carbarsone was mentioned above. Another minor toxic effect — vomiting after the injection of emetine — can be obviated by the use of divided doses. Severer toxic reactions to emetine were noted

TABLE 5. *Data in 6 Cases of Amebic Dysentery Diagnosed Overseas with Relapse in the United States.*

THEATER	COMPLICATIONS	COURSES OF EMETINE	COURSES OF ORAL CARBARSONE	COURSES OF ORAL CHINIOFON	COURSES OF ORAL DIODOQUIN	NO. OF CARBARSONE ENEMAS
China and India-Burma	Diarrhea, watery and bloody stools and ulceration	4	7	2	5	1
Pacific	Diarrhea, watery stools and ulceration	0	1	1	1	0
Pacific	Diarrhea, watery and bloody stools and ulceration	1	2	0	2	0
Pacific	Diarrhea	1	1	0	0	0
Pacific	Diarrhea, watery and bloody stools and ulceration	1	1	1	0	0
Pacific	Diarrhea, watery and bloody stools and ulceration	3	3	0	3	2

is summarized for the 6 patients who had amebic dysentery overseas with relapse in the United States. This table emphasizes the fact that although most of the overseas cases were accompanied by ulceration few patients received retention enemas. In the United States 25 per cent of the men were found to have ulceration and practically all received enemas.

Of the patients who had amebic dysentery overseas 57 per cent developed complications, including 4 cases of ulcerative colitis, 3 of granuloma, 3 of chronic diarrhea, 2 of steatorrhea, 2 of amebic ab-

when injections had been continued for more than seven days or resumed without an adequate rest period. These reactions consisted of localized palsies. In 1 case an abscess of the deltoid muscle followed emetine injections. One man developed exfoliative dermatitis and hepatitis following carbarsone and gave a history of a similar reaction following neoarsphenamine.

AMEBIC HEPATITIS AND AMEBIC ABSCESS

In this group of 105 men 10 had a total of twelve attacks of amebic hepatitis or abscess, not including

cases of hepatomegaly during the course of typical amebic dysentery. Eight of the attacks occurred overseas, and 4 in the United States. All the men had been in the Pacific, China or India-Burma Theater. The diagnostic factors in these cases are summarized in Table 6.

Prompt diagnosis and treatment of amebic hepatitis may prevent the development of abscess formation, and even after the abscess has occurred treatment may cause resolution without operation or drainage. Of the 8 overseas attacks, at least 5 went on to abscess formation, 4 being drained surgically and 1 by spontaneous rupture into a bronchus. Of the 4 cases diagnosed in the United States 2 went on to abscess formation but resolution occurred without drainage. The chief factors in the early diagnosis of amebic hepatitis and abscess are tenderness and enlargement of the liver, with varying degrees of fever and leukocytosis usually without jaundice and often without amebas in the stools. In addition to fixation of the diaphragm there may be x-ray evidence of pulmonary infiltration; consequently, several patients were treated for pneumonia before amebiasis was suspected. The complement-fixation test, which is often positive in amebic hepatitis, may persist long after successful treatment. It is hazardous to wait for laboratory confirmation in dealing with amebic abscess or hepatitis, and the therapeutic response to emetine is sufficiently dramatic to aid in establishing the diagnosis.

The necessity of treating amebic abscess and hepatitis with either carbarsone or one of the iodine containing oxyquinolines is shown clearly in Table 6. The 3 patients treated without adequate oral medication relapsed, 1 with amebic dysentery and 2 with amebic abscess of the liver, whereas the patients given adequate medication did not relapse. Although oral treatment may be deferred until after the course of emetine has been completed, it should not be overlooked when the patient becomes asymptomatic, because the effect of emetine on intestinal amebiasis is only temporary.

Amebic Appendicitis, Granuloma and Rectal Stricture

The incidence of involvement of the appendix in amebic dysentery has been pointed out.[3] In 3 cases of this series attacks of appendicitis might have been caused by amebiasis. In 1 case the cecum as well as the appendix was involved, and twelve days after operation amebas were found. Another man with recurrent liver abscess had an acute abdominal episode when the appendix was removed and found to be ulcerated. One patient had perforation of the cecum and after the appendix had been removed sections showed trophozoites of *E. histolytica*. In 2 of these men the complement-fixation test for amebiasis was positive.

In 3 patients who had amebic dysentery overseas, granulomatous lesions were found on proctoscopic examination in the United States. One man had diarrhea for four months before antiamebic treatment was given; the lesions disappeared after a course of Diodoquin retention enemas. Another patient, who had had several recurrences of amebic dysentery, developed similar lesions, which cleared up when the stools became negative. A patient who did not receive antiamebic therapy until late in the

Table 6. *Data in 10 Cases of Amebic Abscess and Hepatitis.*

Occurrence of Attack Overseas	History of Diarrhea	Maximum Temperature	Tenderness over Liver	Icteric Index	White-Cell Count	Fixation of Diaphragm	Pulmonary Infiltration	Complement-Fixation Test	Source of *E. Histolytica*	Liver Abscess	Rupture or Drainage of Liver Abscess	Emetine Injections	Full Dose of Carbarsone	Diodoquin, Chiniofon or Vioform	Relapse or Complication
		°F.			X10³							days	days	days	
Overseas	No	101	Yes	—	7	No	No	Positive	Pus	Yes	Yes	0	0	0	Amebic abscess
In the United States	No	103	Yes	—	16	No	No	Positive	None	Yes	No	6	0	10	None
In the United States	Yes	99	Yes	—	14	No	No	Negative	None	No	No	6	0	20	None
Overseas	Yes	104	Yes	—	16	No	No	Positive	None	Yes	Yes	0	0	0	Amebic dysentery
In the United States	Yes	100	Yes	—	9	No	No	Negative	None	No	No	6	0	10	None
Overseas	Yes	103	Yes	—	15	Yes	Yes	—	Stool	Yes	No	6	0	7	None
Overseas	Yes	101	Yes	—	22	Yes	Yes	Negative	Sputum	Yes	Yes	10	0	0	Amebic abscess
In the United States	Yes	100	Yes	40	10	Yes	No	Negative	None	Yes	No	8	7	7	None
Overseas	Yes	102	Yes	13	18	No	No	Positive	None	No	No	10	30	20	None
Overseas	Yes	103	Yes	—	22	Yes	Yes	—	Stool	Yes	Yes	7	7	7	None
Overseas	Yes	102	Yes	—	5	No	No	Positive	Stool	No	No	7	7	7	None
Overseas	Yes	104	Yes	—	12	Yes	No	Positive	Stool	No	No	10	6	0	None

course of the disease developed ulcerative colitis and on arrival in the United States had only a few granulomatous lesions that cleared up without further specific therapy. It is interesting to note that at the time of discharge these patients were still subject to recurrent attacks of mild diarrhea brought on by exercise or food indiscretion.

Stricture of the rectum occurred in 1 patient who had severe dysentery with amebiasis discovered after an appendectomy had been performed. Despite several courses of emetine and oral carbarsone he developed stricture of the rectum. The complement-fixation test was positive. The weight fell from 205 to 130 pounds, and the patient died after a colostomy.

TABLE 7. *Schedules for the Treatment of Amebiasis.*

TYPE OF CASE	CONVENTIONAL SCHEDULE			SIMPLIFIED SCHEDULE		
	DRUG USED	DOSE	PERIOD	DRUG USED	DOSE	PERIOD
		gm.	*days*		*gm.*	*days*
Carrier	Carbarsone	0.75	7	Vioform	1.00	10
	Chiniofon or	3.00	7			
	Diodoquin	1.80	7			
Mild amebic dysentery	Carbarsone	0.75	7	Emetine	0.06	6
	Chiniofon or	3.00	7	Vioform	1.00	10
	Diodoquin	1.80	7			
Acute or chronic amebic dysentery	Emetine	0.06	6	Emetine	0.06	6
	Carbarsone	0.75	7	Vioform	1.00	10
	Chiniofon or	3.00	7	Vioform enemas	2.00	5
	Diodoquin	1.80	7			
Severe amebic dysentery	Emetine	0.06	6	Emetine	0.06	6
	Carbarsone	0.75	7	Vioform	1.00	10
	Chiniofon or	3.00	7	Vioform enemas	2.00	5
	Diodoquin	1.80	7			
	Chiniofon enemas or	4.00	5			
	Carbarsone enemas	2.00	5			
Amebic abscess or hepatitis	Emetine	0.06	8	Emetine	0.06	8
	Chiniofon	0.75	7	Vioform	1.00	10
	Diodoquin	1.80	7			

ANTIAMEBIC DRUGS

The sulfanilamide derivatives are mentioned because they are frequently prescribed in the treatment of dysentery of unknown origin. Sulfadiazine or sulfaguanidine was given to 15 men in this series who were subsequently found to have amebiasis. Although in some cases the original illness may have been bacillary dysentery that provoked or was followed by amebic dysentery, in others it is likely that the sulfanilamide derivatives caused a temporary improvement in the amebic infection. Most of the patients with undiagnosed dysentery treated with the sulfonamides relapsed with typical amebic dysentery — 1 with amebic hepatitis.

The conventional schedule for the treatment of amebiasis is based on a combination of three different types of drugs — emetine, carbarsone and iodine containing oxyquinoline (Table 7). Carriers and patients with mild enteric symptoms were given 0.75 gm. of carbarsone daily for a week, followed by 3.0 gm. of chiniofon or 1.8 gm. of Diodoquin daily for another week. Patients with acute and chronic cases of amebic dysentery were given the same treatment, with the addition of 0.06 gm. of emetine daily for six days. In refractory cases and when ulcers are visible the use of chiniofon or carbarsone retention enemas is also recommended. In amebic abscess and hepatitis the emetine is prolonged for a total of eight days, and carbarsone is omitted. This regime, although it was followed closely overseas, led to a relapse rate of 40 per cent in this selected group of cases. Furthermore, diarrhea medicamentosa was frequently noted, especially with chiniofon but also with carbarsone.

Recent studies of blood iodine levels suggest that vioform is the best of the available iodine-containing derivatives of oxyquinoline.[4] Unfortunately, an erroneous statement in the literature that vioform is irritating when given rectally[5] has been repeated in textbooks and has deterred physicians from employing retention enemas of vioform or Diodoquin. This report was incorrectly based on a previously reported experiment in which the hydrochloric acid derivative of vioform was used.[6] Vioform is now available in a powdered form that makes an excellent suspension in tap water and is not irritating even when given to patients with severe amebic or ulcerative colitis. Diodoquin, which is also nonirritating, must be powdered before it can be suspended in water. When vioform is used rectally 200 cc. of a 1 per cent suspension is given on alternate nights for five doses.

With a knowledge of the chemical stability and nonirritating properties of vioform a new schedule of treatment has been devised (Table 7). This schedule calls for 1.0 gm. of vioform daily for ten days, instead of both carbarsone and chiniofon. Emetine is given in all symptomatic cases, and retention enemas of vioform are given concurrently with the oral course of this drug in all but the mildest cases of amebic infection. This schedule of treatment has been effective in the most resistant cases of amebic dysentery, including those from the India-Burma Theater, and has abolished diarrhea medicamentosa (Table 8).

Ulcerative Colitis

Five patients in this series were admitted to the hospital with a diagnosis of ulcerative colitis. Four had served overseas in the Pacific Theater, and 1 had never been outside the United States.

One patient gave a history of both amebic and bacillary dysentery, 3 gave a history of amebic dysentery without any known bacillary dysentery, and the patient who had not been overseas gave a history of undiagnosed dysentery acquired during an epidemic.

Three of the cases that occurred after amebic dysentery were extremely mild, and 1 was severe.

Table 8. *Incidence of Diarrhea with Antiamebic Drugs Used in the United States.*

Drug	Route	No. of Cases	No. of Cases with Diarrhea
Chiniofon	Oral	3	2
Carbarsone	Rectal	4	1
Carbarsone	Oral	32	4
Diodoquin	Rectal	2	0
Diodoquin	Oral	36	0
Vioform	Rectal	4	0
Vioform	Oral	12	0

The other case, although not severe, had relapsed several times.

These men were all given a course of sulfadiazine, and 3 of them were also given a course of vioform. Four patients recovered, and 1 who failed to improve was transferred to another hospital.

Chronic Diarrhea

The term chronic diarrhea is used to describe a condition that does not fit any other clinical syndrome. The condition, which is characterized by recurrent, self-limited attacks of mild diarrhea, is usually brought on by exercise, spiced foods or alcoholic beverages. It does not include ulcerative colitis, mucous colitis or patients with psychiatric disorders. The final diagnosis was chronic diarrhea in 10 cases in this series. Actually the incidence of this condition was greater, but when a diagnosis of amebic dysentery was made in the United States the recurrent diarrhea was considered a residual symptom of amebic infection and a diagnosis of chronic diarrhea was not made. This syndrome was also noted among persons on the hospital staff who had been overseas and had been evacuated to this country under the rotation policy.

Most of the men with chronic diarrhea had served in the Pacific, China or India-Burma Theater. All had a history of intestinal disease, and in 80 per cent a definite diagnosis of amebic dysentery had been made. One of the men suffering from chronic diarrhea had been infected with strongyloides and developed diarrhea when he was given gentian violet. In some cases the diarrhea was aggravated by treatment with carbarsone. About half the men had hookworm infestation, and some had received several courses of tetrachlorethylene. Other possible factors in the production of this syndrome included exposure to the hardships and food conditions of overseas installations, especially in the combat zone. In these cases the diarrhea was often accompanied by cramps and a feeling of malaise that cleared up when the attack subsided. There was usually relatively slight weight loss. Physical examination was not remarkable except for tenderness over the colon or small intestine. Laboratory studies were entirely negative, including x-ray examination of the gastrointestinal tract, twenty-four-hour-stool fat analysis, microscopic examination of the stool and repeated rectal cultures.

Most of the patients with chronic diarrhea were not given any specific therapy and showed gradual improvement with rest and diet. Sulfadiazine was tried in a few cases without benefit. Vioform, which caused considerable improvement in the 2 cases in which it was given, deserves further trial when there is a history of amebic infection.

Steatorrhea

Most studies of fat excretion have been based on a chemical partition of the dried stool. It is known that 5 to 10 per cent of ingested fat is excreted, however, so that with a normal intake of 100 gm. of fat the twenty-four-hour stool should not contain more than 10 gm. of fat.[7] It is also known that diarrhea of any type may cause an increase in fat excretion but that more marked disturbances occur in pancreatic disease and sprue. For the purposes of this study a twenty-four-hour stool specimen was deemed adequate because of the presence of diarrhea. An aliquot of the moist stool was analyzed for total fat by the Fowweather method.[8]

Table 9. *Approximate Total Fat Excretion in Twenty-Four Hours on a Diet of 100 Gm. or Less of Fat.*

Clinical Diagnosis	Weight of Stool	Percentage of Fat	Fat Excreted
	gm.		gm.
Pancreatogenous steatorrhea	866	9.2	80
Sprue	1949	3.7	74
Sprue	1050	4.5	47
Sprue	298	12.1	36
Sprue	522	6.0	31
Sprue	1004	1.8	18
Ulcerative colitis	671	2.4	16
Sprue	712	2.2	16
Sprue (convalescent)	412	2.9	12
Cholecystitis (convalescent)	278	3.3	9
Chronic diarrhea	315	2.6	8
Chronic diarrhea	249	2.8	7
Malocclusion	176	3.8	7
Diarrhea from carbarsone	363	1.6	6
Amebic dysentery	242	2.2	6
Chronic diarrhea	253	1.4	5
Ulcerative colitis	563	0.8	5
Mucous colitis	170	2.8	5
Mucous colitis	270	1.5	4
Chronic diarrhea	223	1.8	4
Normal control	192	1.8	3
Chronic diarrhea	302	1.1	3
Normal control	110	2.2	2
Normal control	85	1.5	1
Malocclusion	44	2.6	1
Mucous colitis	52	2.0	1

The total fat excretion in twenty-four hours was measured in 26 cases (Table 9). Normal persons excreted 1 to 5 gm. Patients with mild diarrhea excreted 3 to 9 gm. There were 9 patients who excreted 12 to 80 gm., including 1 with ulcerative colitis, 1 with pancreatogenous steatorrhea and 7 with a syndrome closely resembling tropical sprue.

Pancreatogenous diarrhea may be differentiated from sprue by several laboratory tests. In sprue the stool is bulky, there may be a lowering of the serum calcium and phosphorus, as well as the hemoglobin, and the glucose-tolerance test tends to be flat. In pancreatic disease the stool contains undigested meat particles and an increased amount of nitrogen; there may be an increase in the serum amylase, and the glucose-tolerance test may be elevated. The only case of pancreatogenous steatorrhea in this series showed all the abnormalities mentioned.

Sprue

One of the characteristic features of sprue is that it occurs at a variable period after a person has left the tropics.[9] It seems quite likely that steatorrhea begins long before the development of classic sprue, since it takes some time to deplete the mineral and vitamin stores. This intermediate stage in the development of sprue has been called presprue or incomplete sprue.[10] Of the 7 cases in this study only 2 were diagnosed overseas.

The case histories showed several common characteristics (Table 10). All the men had served in New Guinea or the Philippines. The latter location is a well known source of a spruelike disease that has been considered a complication of amebiasis.[11] The period of exposure in the tropics varied from one to three years. All the men gave a history of dysentery, and amebic infection was proved in 2 cases. The average weight loss amounted to 47 pounds.

Associated with the weight loss these patients showed wasting of the musculature, looseness of the skin and marked pallor. Transient soreness and redness of the tongue in 5 of the 7 men went on to ulceration in a few cases. Gaseous distention and abdominal tenderness were frequently noted. Proctoscopic examination showed hyperemia in 4 cases. X-ray studies disclosed redundancy of the colon in 3. One man developed a peripheral neuritis.

The total bulk of the twenty-four-hour stool was markedly increased, with an average weight of 850 gm. The stool was light in color and varied from soft to liquid, with a tendency to adhere to the glass container. The total fat excretion was markedly increased, averaging 36 gm.

Gastric analysis revealed the presence of a variable amount of free acid in all cases. The serum proteins were normal or slightly less than normal. In a few cases the blood calcium and phosphorus were below normal. The average red-cell count was 4,200,000, and the average hemoglobin 12.5 gm. The glucose-tolerance test showed a marked tendency to be low and flat; the average maximum value after 100 gm. of glucose was only 115 mg. per 100 cc.

Of the 2 patients in whom a diagnosis of sprue was made overseas only 1 was given a low-fat diet and liver extract. This man showed marked improvement and was convalescent when he arrived in the United States. The other patients were in poor condition, despite the fact that some of them had learned to avoid fatty food.

In the United States the patients were put on a strict low-fat diet. The regular hospital diet contained 100 gm. of fat, the high-calorie diet 150 gm. and the strict low-fat diet only 40 gm. In this diet the rest of the calories were furnished by 400 gm. of carbohydrate and 120 gm. of protein. In addition to the diet, each patient was given 5 cc. of crude liver extract twice weekly. On this regime the diarrhea improved, the cramping ceased, and there was a rapid weight gain. It was not possible to follow all these patients, but 4 were well enough to be discharged from the hospital, 2 were sent to convalescent hospitals and 1 was transferred to another general hospital.

Although the eventual prognosis in these cases cannot be determined, it is possible that the development of classic sprue was prevented by early treatment of the underlying metabolic disturbance, that is, steatorrhea.

Hookworm Infestation

Of the 45 cases of hookworm infestation in this series 13 were diagnosed overseas only, 16 were diagnosed overseas and in the United States, and 28 were diagnosed for the first time in the United States. Almost all the men were exposed in the Pacific Theater. These figures do not give a fair picture of the incidence of infestation, however, because the entire group was specially selected from the enteric disease ward.

None of the men observed in the United States had symptoms that could be ascribed to hookworm infestation. There is no doubt that symptomatic hookworm disease was encountered overseas, but sufficient treatment was given to clear the symptoms before the patients returned to the United States.

In the cases that were diagnosed overseas and were not complicated by other parasites, the average eosinophil count was 16 per cent. When these men arrived in the United States those with negative stool findings had an average eosinophil count of 2 per cent, and those with positive stool findings had an average eosinophil count of 13 per cent. In cases diagnosed in the United States for the first time the average eosinophil count was 9 per cent. The total white-cell count was sometimes increased, the maximum noted in this series being 18,000.

Overseas the treatment for hookworm infestation consisted almost entirely of tetrachlorethylene in doses of 3 cc. In some cases the drug was given in larger doses, and in some, hexylresorcinol was employed.

The results of hookworm treatment are shown in Table 11. About half the men treated overseas were found to have negative stools, and about half were found to have positive stools when they arrived in the United States, regardless of the number of treatments that had been given. Treatment in the United States gave similar results, even when the dose of tetrachlorethylene was increased to 4 cc. and 1 cc. of oil of chenopodium was added.

Although tetrachlorethylene was no more effective in the United States than overseas, few patients received more than two courses of the drug even when the stools remained positive, and some patients were not held in the hospital long enough to determine whether ova were still being excreted. This indicates that the policy on the gastrointestinal ward was to limit retreatment to one course of tetrachlorethylene. Inasmuch as hookworm infestation is self-limited, this policy was considered safe and in fact beneficial to the patient.

TABLE 10. *Data in 6 Cases of Sprue Contracted in the Pacific Theater.*

Overseas Service	Chief Symptoms Overseas	Chief Treatment Overseas	Transfer Diagnosis Overseas	Condition of Tongue	Proctoscopic Examination	Barium-Enema Examination
mo.						
16	Diarrhea and vomiting	Antiamebic and dietary	Dysentery (unclassified)	Atrophic	Negative	Redundant colon
34	Diarrhea and vomiting	Transfusion and vitamin	Malnutrition and anemia	Sore and reddened	Negative	Negative
23	Diarrhea and vomiting	Sulfonamides	Dermatitis	Sore and reddened	Hyperemia of mucosa	Negative
27	Cramps and vomiting	Dietary	Sprue	Red and ulcerated	Hyperemia of mucosa	Redundant colon
25	Diarrhea and vomiting	Antiamebic	Dysentery (unclassified)	Normal	Previous ulceration	Negative
15	Diarrhea and cramps	Antiamebic and sulfonamides	Amebic dysentery	Sore and reddened	Hyperemia of mucosa	Negative
22	Diarrhea and cramps	Dietary	Sprue	Sore and reddened	Hyperemia of mucosa	Redundant colon

STRONGYLOIDIASIS

Strongyloidiasis was found in 12 men from the Pacific Theater, in 2 from the China and India-Burma theaters and in 2 from the European Theater. Most of the diagnoses were made from routine stool examinations, but some were arrived at only after repeated studies made to find the cause of eosinophilia. In 1 case the long series of negative examinations that preceded the first positive findings may have been associated with the incubation period. The patient, who was overseas in April and May, returned in June with a white-cell count of 14,000, with 43 per cent eosinophils. Repeated stool examinations were negative until the middle of July, when larvae of strongyloides were found.

Only 5 of the 16 patients with strongyloidiasis were asymptomatic (Table 12). Eleven men complained of cramps, and 5 were also troubled with diarrhea. Tenderness on abdominal palpation was a frequent finding.

It is interesting to note that the patient was cured in only 1 of the 10 cases discovered overseas. This may in part have been due to the fact that enteric-coated gentian violet was not generally available outside this country. Of the patients treated in the United States, however, at least 2 still had positive stool findings at the time of discharge. One of these men had received intravenous and intraduodenal gentian violet, as well as a thirty-day course of the oral preparation.

The situation is further complicated by the fact that strongyloidiasis is a self-perpetuating organism.[12] The need for further observation and study of this disease is obvious.

BACILLARY DYSENTERY

No patients with active cases of bacillary dysentery were admitted to the hospital in the United States during the course of these studies. One carrier of Shigella organisms was found who had had bacillary dysentery while in the Pacific Theater.

Three other patients in this series had bacillary dysentery overseas, but stool and rectal cultures were negative in the United States.

One of the men who had had bacillary dysentery, however, developed mucous colitis, and another who had had both bacillary and amebic dysentery developed ulcerative colitis. There were no other cases of enteric disease following bacillary dysentery, despite its widespread occurrence overseas.

Miscellaneous Parasites

Six proved cases of schistosomiasis are included in this series because of concomitant amebiasis. Four of these patients were found to have ova in the stools both overseas and in the United States, whereas stool examinations in 2 cases were positive overseas but negative in the United States. In 4 cases a clinical diagnosis of schistosomiasis had been made overseas, but since ova were not found overseas or in the United States the diagnosis is not certain. It is interesting to note that no carriers or mild cases of schistosomiasis were found in patients admitted to the hospital with a diagnosis other than schistosomiasis. All the patients with schistosomiasis were transferred to a special ward for treatment and follow-up study after the amebiasis had been brought under control.

Five of the men in this group were found to have ascariasis and were treated overseas; they were stool negative on arrival in the United States. Five other patients treated in the United States for the first time were also cured after one or two courses of hexylresorcinol.

There were several asymptomatic carriers of *Trichuris trichura*, *Giardia lamblia* and *Trichomonas hominis*. No treatment was given to these patients.

Summary

The records of 105 patients studied on the gastrointestinal ward of a general hospital are analyzed. Attention is drawn to the latent and chronic nature of the diarrheal diseases acquired while the patient was serving outside the United States.

Carriers of *Entamoeba histolytica* should be treated to prevent the subsequent development of dysentery. The importance of sigmoidoscopic examination and the collection of purged stools in the diagnosis of amebiasis is emphasized. The need for early clinical diagnosis in amebic hepatitis and for prompt treatment with emetine, as well as with further medication with carbarsone or one of the iodine containing oxyquinolines, is stressed. Tissue invasion, usually evidenced by a positive complement-fixation test, may produce stricture of the rectum and appendicitis, as well as granulomatous lesions.

Patients with amebic dysentery who show any evidence of rectal involvement — either by proctoscopic examination or from the presence of blood in the stools — should be treated with retention enemas. Contrary to current belief, vioform suspension is nonirritating and most convenient for retention enemas in the treatment of amebic dysentery. It is advisable to give an oral course of this drug in conjunction with retention enemas, thus obviating the use of chiniofon and carbarsone, which are likely to aggravate diarrhea.

Table 10. *Data in 6 Cases of Sprue Contracted in the Pacific Theater (Continued).*

Weight Loss	Total Stool Fat	Maximum Free Gastric Acid	Serum Albumin	Serum Globulin	Red-Cell Count	Hemoglobin	Glucose-Tolerance Test (Maximum)	Response to Strict Low-Fat Diet/Art
lb.	*gm.*	*units*	*gm./100 cc.*	*gm./100 cc.*	*X10⁶*	*gm./100 cc.*	*mg./100 cc.*	
62	73.6	15	4.4	1.2	4.1	12.1	95	Excellent
45	18.1	—	5.4	1.0	3.6	10.5	132	Good
53	46.8	12	5.4	1.0	4.7	13.9	108	Excellent
57	36.1	55	5.4	2.3	4.9	13.0	103	Good
13	31.2	44	—	—	4.5	12.9	150	Good
29	15.7	40	5.1	1.1	4.9	14.3	137	Good
69	11.9	49	—	—	3.2	10.8	95	Excellent

Ulcerative colitis apparently develops after severe amebic dysentery as well as after bacillary dysentery. Men who have served overseas, especially those who have had amebic dysentery, are subject to recurrent attacks of diarrhea. This condition responds gradually to rest and diet and is sometimes helped by antiamebic treatment.

A large proportion of cases considered as unclassified dysentery will be found to have steatorrhea on analysis of the twenty-four-hour stool for fat. Stool analysis can be simply accomplished by wet extraction. Most cases of steatorrhea correspond to early stages in the development of sprue, and despite the loss of a great deal of weight there may be no signs of vitamin deficiency. These patients respond well to a diet strictly limited in fat and high in protein and carbohydrate.

TABLE 11. *Results of Hookworm Treatment.*

Overseas			In the United States			
No. of treatments	Positive stool examination in United States	Negative stool examination in United States	No. of treatments	Positive stool examination	Negative stool examination	Not followed
1	7	8	1	3	5	3
2	3	3	2	4	2	2
3	1	0	3	1	0	0
4	1	1	4	1	0	0
5	0	0	Variable*	5	3	2
6	1	0				
7	2	0				
8	1	0				
9	0	0				
10	0	1				
Totals	16 (55%)	13 (45%)		14 (45%)	10 (32%)	7 (23%)

*Increased dose of tetrachlorethylene, as well as oil of chenopodium.

Hookworm infestation is frequent in troops from the Pacific area. Symptoms from this infestation are rare, and although treatment with tetrachlorethylene may not eradicate all the parasites it is not necessary to continue treatment after two courses of the drug have been given. Strongyloidiasis when it occurs may cause marked eosinophilia suggesting schistosomiasis. Treatment with gentian violet is not always effective, and the need for further study is suggested.

TABLE 12. *Data in 16 Cases of Strongyloidiasis.*

	Data Overseas							Data in United States								
Theater	Symptoms	Positive stools	White-cell count	Eosinophils	Gentian violet		Route employed	Symptoms	Positive stools	White-cell count	Eosinophils	Chief clinical diagnosis	Gentian violet		Route	Positive stool examination after treatment
					Dose	Period							Dose	Period		
			x^3	%	*mg./day*	*days*				x^3	%		*mg./day*	*days*		
Pacific	Yes	Yes	7	26	125	4	Intravenous	Yes	Yes	8	2	Strongyloidiasis	180	10	Oral	Yes
					250	3	Intraduodenal						300	5	Oral	Yes
													180	30	Oral	Yes
European	Yes	Yes	9	9	—	-	—	Yes	Yes	14	4	Strongyloidiasis	180	10	Oral	No
Pacific	Yes	Yes	11	60	—	-	—	Yes	Yes	11	29	Strongyloidiasis	300	5	Oral	Yes
													180	10	Oral	No
Pacific	Yes	No	32	69	—	-	—	Yes	Yes	10	7	Strongyloidiasis	180	10	Oral	No
Pacific	No	—	—	—	—	-	—	No	Yes	10	12	Strongyloidiasis	180	10	Oral	No
Pacific	Yes	No	30	62	—	-	—	Yes	Yes	8	1	Strongyloidiasis	180	10	Oral	No
Pacific	No	—	—	—	—	-	—	Yes	Yes	14	3	Strongyloidiasis	180	10	Oral	Yes
													300	5	Oral	Yes
													180	30	Oral	Yes
Pacific	Yes	Yes	8	24	125	3	Intravenous	Yes	Yes	7	21	Strongyloidiasis	180	10	Oral	No
Pacific	Yes	Yes	7	20	—	-	—	Yes	Yes	10	28	Strongyloidiasis	180	10	Oral	No
Pacific	Yes	Yes	10	21	250	4	Intraduodenal	Yes	No	7	4	Steatorrhea	—	—	—	No
Pacific	No	Yes	—	—	—	-	—	No	Yes	9	12	Strongyloidiasis	180	10	Oral	No
Pacific	Yes	Yes	8	36	180	30	Oral	Yes	Yes	9	12	Strongyloidiasis	180	10	Oral	No
China and India-Burma	No	—	—	—	—	-	—	No	Yes	13	32	Strongyloidiasis	180	10	Oral	No
China and India-Burma	No	—	—	—	—	-	—	No	Yes	12	5	Strongyloidiasis	180	10	Oral	No
European	Yes	Yes	8	4	250	1	Intraduodenal	Yes	Yes	8	6	Strongyloidiasis	180	10	Oral	No
					180	30	Oral									
Pacific	No	Yes	19	60	180	12	Oral	No	Yes	9	35	Strongyloidiasis	180	10	Oral	No
					160	1	Intraduodenal									

Bacillary dysentery and other intestinal parasite infections, with the exception of schistosomiasis, did not present any special problems in diagnosis or treatment.

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References

1. Craig, C. F. *The Etiology, Diagnosis, and Treatment of Amebiasis.* 332 pp. Baltimore: Williams & Wilkins Company, 1944. P. 284.
2. Craig.[1] P. 251.
3. Craig.[1] P. 168.
4. David, N. A., Phatak, N. M., and Zener, F. B. Iodochlorhydroxyquinoline and diodohydroxyquinoline: animal toxicity and absorption in man. *Am. J. Trop. Med.* 24:29-33, 1944.
5. Anderson, H. H. Amebiases — important aspects of its treatment. *California & West. Med* 42:340-345, 1935.
6. Anderson, H. H., and Reed, A. C. Untoward effects of anti-amebic drugs. *Am. J. Trop. Med.* 14:269-281, 1934.
7. Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry.* Vol. I. *Interpretations.* 1264 pp. Baltimore: Williams & Wilkins Company, 1931. P. 234.
8. *Idem. Quantitative Physical Chemistry.* Vol. 2. *Methods.* 957 pp. Baltimore: Williams & Wilkins Company, 1932. P. 490.
9. Manson-Bahr, P. H. *The Dysenteric Disorders: The diagnosis and treatment of dysentery, sprue, colitis and other diarrhoeas in general practice.* Second edition. 629 pp. Baltimore: Williams & Wilkins Company, 1943. P. 246.
10. Manson-Bahr.[9] P. 368.
11. Craig.[1] P. 178.
12. Faust, E. C. *Human Helminthology: A manual for physicians, sanitarians and medical zoologists.* Second edition. 780 pp. Philadelphia: Lea & Febiger, 1939. P. 396.

SURGICAL TREATMENT OF ASCITES

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Ascites is a problem frequently encountered and often unsatisfactorily treated. An adjunct in the therapy of ascites has been tried in a limited number of cases and has seemed sufficiently helpful to warrant reporting.

Attempts to obtain more lasting relief from ascites have been many and varied. In 1896 Drummond and Morison[1] reported the first surgical treatment of ascites. Talma,[2] in 1898, is usually credited with the original suggestion for the surgical relief of ascites, and the operation — omentopexy — has come to be known as the Talma–Morison operation. Morison's patient lived two years after the operation. Monprofit[3] reported 224 cases treated by the Talma–Morison operation up to 1904. Thirty-one per cent of this group were successfully relieved of their ascites for varying periods. Noetzel,[4] in 1919, and Mayo,[5] in 1924, reported smaller groups in which the operative mortality was high and good results relatively few. Hughson[6] considered the operation to be without value. Grinnell[7] obtained relief from ascites in only 2 of 23 patients operated on. In 1943 Cates[8] reviewed the patients treated by omentopexy at the Los Angeles County Hospital during the previous five years. Thirty-eight patients who were operated on were compared with 172 treated medically; follow-up study led to the conclusion that the surgical intervention did not improve the prognosis. Operative mortality was high: 42 per cent of the patients died within two weeks of the operation, presumably because of undernutrition, the susceptibility of patients with cirrhosis of the liver to shock and tympanites, poor wound healing associated with hypoproteinemia, and the greater danger of administering anesthesia because of failure of the cirrhotic liver to detoxify the anesthetic agent.

The operation itself is a simple one. An epigastric incision is made just to the right of the midline through the abdominal wall, the peritoneal cavity is opened, and a portion of the omentum is withdrawn. A second lower incision is made through the skin and muscle down to the posterior aponeurosis and peritoneum. The rectus muscle is separated from its posterior attachment, and the omentum is drawn from the upper incision down into the extraperitoneal pocket thus formed. The rationale is simply to establish a portal collateral circulation via the omentum and the vessels of the abdominal wall. All the earlier attempts at surgical control of ascites were somewhat impeded by failure to take into consideration and to treat adequately other contributory factors, such as hypoproteinemia and poor liver function. Evaluation of omentopexy over a long period, however, seems to indicate that it leaves much to be desired.

Another attempt at the surgical treatment of ascites is described by Ferguson,[9] who reports a case in which a right nephrectomy was performed and the renal pelvis anastomosed to the peritoneum along the peritoneal gutter beside the ascending colon. Since omentum blocked the outlet in this position, the site of anastomosis later had to be shifted to the lower part of the right rectus muscle. This, of course, simply provided an outlet for the ascitic fluid via the bladder and thus obviated repeated paracenteses. The protein content of the fluid, however, was still lost to the patient.

A third method, aimed at relieving the portal hypertension of cirrhosis, is described by Blakemore and Lord[10] and by Whipple.[11] In 5 cases the blood was shunted from the portal to the caval system by removal of the spleen and left kidney and by

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anastomosis of the splenic and left renal veins by means of an endothelial-lined vitallium tube. In 5 other cases portacaval shunts (Eck fistulas) were produced by end-to-side anastomoses of the portal vein to the inferior vena cava over vitallium tubes and ligation of the portal vein between operations. Whipple stated that all 10 patients survived the operation but that a follow-up period of three years or more would be required to determine the value of these portacaval shortcircuiting procedures.

The method of treating ascites described below is by the insertion of a glass button into the abdominal wall. The origin of this therapeutic device is obscure. It was first encountered by one of us (R.C.C.) in New Orleans, where it was used by Dr. Julian Rickles,[12] who, in turn, had heard about it from Dr. Douglas Donath,[13] who had been using it at the Marine Hospital in New Orleans. Communication with Dr. Donath revealed that he, too, had tried to ascertain the origin of the glass button and had traced it as far as a British Army surgeon in Egypt but had been unable to learn the name of its originator. One reference to the use of a similar device was found in the literature. Tannahill,[14] in 1930, reported a single case of cirrhosis of the liver with ascites treated by the insertion of two glass buttons — one under the sheath of the upper rectus muscle and the other lateral to it in the upper quadrant. These were smaller buttons than those used by us, and Tannahill called them "Paterson buttons." He attributed the idea to Professor Peter Paterson, of Glasgow University. His patient required one postoperative paracentesis but subsequently did well.

Lichtman[15] states that in 1922 Boccaro used a glass tube resembling a collar button to drain ascitic fluid into the subcutaneous tissues. This reference was not found in the literature.

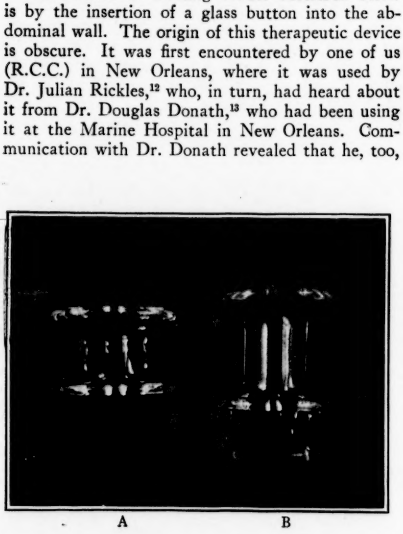

FIGURE 1. *Abdominal Buttons.*

A — *the button used by former workers.* B — *the button with an added glass plate to prevent omental impaction in the core.*

The button as used by previous workers is shown in Fig. 1*A*. We have added the top plate, as shown in Fig. 1*B*. The button can be made by any competent glass blower. The flanges are approximately 2.0 cm. in diameter, and the bore is 0.6 cm. The button itself varies from 1.0 to 1.5 cm. in length, and the added glass plate lies approximately 0.6 cm below the lower flange.

This button is inserted into the anterior rectus sheath, the lower flange, with the glass plate, lying just inside the peritoneum. The rectus sheath fits between the flanges, and the distance between the flanges can be varied to accommodate various thicknesses of the sheath in different patients. The anterior rectus sheath is sutured tight under the upper flange, and the skin closed. The function of the button is simple: it merely allows ascitic fluid to pass through its core and thus into the subcutaneous tissues, where it is absorbed as edema fluid. We have added the top plate in an attempt to prevent the omentum from blocking the outflow of ascitic fluid by becoming impacted in the core of the spool as happened in some cases in which it was used in New Orleans.[12]

One great advantage of this therapeutic device is its ease of application. It is known that patients with hepatic cirrhosis do not tolerate major surgery well. Malnutrition, susceptibility to shock and tympanites contribute greatly to the high operative mortality. Secondly, wound healing is poor unless vitamin C and a great deal of protein, preferably as intravenous plasma or amino acids, are given. Finally, the anesthetic tolerance is poor, since the damaged liver detoxifies the anesthetic agent poorly; yet large amounts of anesthetic are usually required for satisfactory anesthesia in patients with alcoholic liver cirrhosis. For these reasons major surgical procedures such as those outlined above are at best limited in their applicability.

The insertion of the button is a simple procedure and may be done under local anesthesia if desired, although spinal anesthesia was used in all our cases. The site selected may be over either the right or the left rectus muscle below the level of the umbilicus. A 6 cm. midrectus incision is made and deepened through the muscle layer to the peritoneum, which is nicked to allow the insertion of a suction tube to remove the ascitic fluid. The opening in the peritoneum is then made the same length as the skin incision. The peritoneum and anterior rectus fascia at the lower margin of the wound are grasped with an Ochsner clamp, and the fat layer below the lower end of the wound freed up over an area from 8 to 10 cm. below the lower margin of the wound. After retraction of the skin and fat layer at the lower part of the wound downward and pulling upward on the Ochsner clamp

holding the peritoneum and anterior rectus fascia, a stab wound is made about 4 cm. below the lower margin of the wound going through the anterior rectus fascia, muscle and peritoneum. The stab wound is enlarged enough to allow for the insertion of the button. A silk purse-string stitch is then taken in the peritoneum around the button to fix it in place; a similar stitch is taken in the anterior rectus fascia after the rectus muscle has been placed between the flanges of the button. The main wound is then closed in layers without drainage.

Ideally, of course, sufficiently good treatment of the underlying disease so that ascites disappears spontaneously is the goal of therapy. Unfortunately, such a result is not always or even often possible; diuretics and repeated paracenteses are the rule. The mechanism of the production of ascites in cirrhosis is not entirely clear. It has been suggested that ascites is the result of hypoproteinemia, although the relation between ascites and the serum protein or albumin level is not always a parallel one. It has also been suggested that ascites is the direct result of portal hypertension — a hypothesis difficult to prove or disprove. The theory of Ralli et al.[16] that the ascites is due to an antidiuretic hormone — possibly to failure of the diseased liver to destroy posterior pituitary antidiuretic hormone — is an interesting concept that fails, however, to explain the absence of edema in many patients with definite ascites.

The avoidance of repeated paracenteses is the purpose of the abdominal button, which is a purely symptomatic measure but has another advantage: it returns to the patient his own ascitic fluid together with its protein content. The protein loss from repeated paracenteses is not inconsiderable. In some clinics it is the practice to reinject the ascitic fluid intravenously so that the protein content will not be lost to the patient. The abdominal button does this automatically; the ascitic fluid draining through the core of the button becomes edema fluid as fast as it is formed and is absorbed as such. Thus the button may be regarded as a mechanism by which the patient with ascites is given a constant slow clysis of his own ascitic fluid so long as such fluid is formed.

This procedure was employed in 7 cases. One recent case is not included in this report. The following case report is typical.

Case 2. W. D. (P.D.H. 14-421), a 48-year-old food broker entered the hospital on April 23, 1945. The alcoholic intake had averaged a quart of Bourbon whisky daily for many years. During the previous year food intake had been confined to a small evening meal daily. In May, 1942, a Civil Service physical examination had been negative. Except for a bleeding hemorrhoid in October, 1942, the patient remained well until the winter of 1944–1945, when he began to feel weak and tired. He lost 20 pounds in weight during the winter, and 5 weeks before admission he developed an upper respiratory infection, with general malaise, followed a week later by jaundice. At that time he completely lost his appetite, the food intake being confined to fruit juices. Alcohol was not used. Self-administered "salts" for several days produced diarrhea and rectal bleeding. Bowel movements were otherwise light in color, the urine was dark and there was progressive swelling of the abdomen. Four days before admission abdominal paracentesis yielded 6 liters of fluid. Following this there were dysphagia and nausea, and a small amount of blood was vomited.

Examination revealed an obese, deeply jaundiced and rather acutely ill and confused man. The heart and lungs were essentially normal. The abdomen was tense and protuberant, extending well above the costal margin. There were shifting dullness and a fluid wave. The liver was palpated 4 fingerbreadths below the right costal margin. The spleen was not felt. No edema was noted. Spider telangiectases were present.

Examination of the urine showed a + test for albumin, a ++++ test for bile and approximately 1 white cell and 1 red cell per high-power field. Examination of the blood showed a red-cell count of 3,340,000, with a hemoglobin of 64 per cent, and a white-cell count of 20,500, with 90 per cent neutrophils, 31 per cent of which were band cells. The serum bilirubin was 28 mg. per 100 cc., 21 per cent of which was direct, the nonprotein nitrogen was 36 mg., the total protein 5.9 gm., the albumin 2.9 gm. and the globulin 3.0 gm. per 100 cc. The blood Hinton test was negative. The sedimentation rate was 29 mm. in 1 hour. The stools gave ++++ benzidine and guaiac reactions. The bromsulfalein test showed 98 and 82 per cent retention of the dye at 30 and 60 minutes respectively. A cephalin-flocculation test was +++ in 24 hours. Two weeks later the total protein was 5.5 gm., the albumin 1.7 gm. and the globulin 3.8 gm. per 100 cc., and the bromsulfalein test showed 67 and 48 per cent retention of the dye at 30 and 60 minutes respectively. The cephalin-flocculation test was ++ in 24 hours. The serum bilirubin was 24.8 mg. per 100 cc. indirect and 19.8 mg. direct. The prothrombin time was 50 per cent normal throughout.

The patient was given a high-protein, high-carbohydrate, low-fat, low-salt diet, with 57.6 gm. of powdered yeast three times daily and supplementary thiamine chloride and vitamin B complex by injection. Crude liver extract and vitamin K were also given by injection. Ammonium chloride and Mercupurin provided a fair diuresis. Abdominal paracentesis was discontinued after 900 cc. of fluid had been removed, but drainage continued for several days, a total of 8 pounds in weight being lost during the hospital stay. The patient was discharged only slightly improved and advised to remain on diet and vitamin therapy.

Following discharge the hepatitis improved slowly but steadily. The color of the stools became normal, the urine became lighter, and the patient felt somewhat improved. Repeated abdominal paracenteses were required, however, to control the ascites, and for this reason on July 13, after the jaundice and hepatitis had almost disappeared, an abdominal button was inserted under spinal anesthesia. The postoperative course was uneventful. On getting up the patient developed marked edema of the thighs, scrotum and penis, despite the fact that all the ascitic fluid had been aspirated at the time of operation. This edema was gradually absorbed, however, but when the patient was last heard from slight edema was noticed (evidence that ascitic fluid was still forming but was draining via the button). Shortly after the operation he reported that he felt better than he had in years. Six months postoperatively he was completely symptom free, except for minimal edema of the lower abdominal wall, had resumed full activities and had regained his normal weight and strength.

A summary of the data and results in all 6 cases is presented in Table 1. As can be seen the 5 cases were fairly typical of Laennec's cirrhosis in various stages of compensation. Four patients had been confirmed alcoholic addicts for many years. The patient in Case 5 denied the use of alcohol, and the dietary history as given was adequate; yet the clinical picture left little doubt of the diagnosis. All patients showed typical spider telangiectases, and all had low serum proteins, with reversal of the albumin-globulin ratio. The prothrombin time was significantly prolonged in all except Case 4, and bromsulfalein retention was marked in all

TABLE 1. *Data and Results in 6 Cases in Which the Abdominal Button Was Inserted.*

CASE NO.	AGE	SEX	AMOUNT OF ALCOHOL TAKEN DAILY	DURATION OF ALCOHOLISM	DURATION OF ASCITES	DEGREE OF ASCITES	SERUM BILIRUBIN	TOTAL PROTEIN	SERUM ALBUMIN	SERUM GLOBULIN	PROTHROMBIN TIME	BROMSULFALEIN RETENTION*		RESULT OF TREATMENT
												30 MIN.	60 MIN.	
	yr.			*yr.*	*mo.*		*mg./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*sec.*	*% of dye*	*% of dye*	
1	32	M	3 quarts of whisky	15	7	++++	1.5	6.0	1.7	4.3	46 (control, 23)	89	88	Patient symptom free and taking part in full activities 11 mo. after operation
								6.2	3.1	3.1		35	16	
								7.7	4.5	3.2		20	9	
								7.3†	5.0†	3.3†	Normal†	11†	4†	
2	48	M	1 quart of whisky	Many	1	++++	28.0	5.9	2.9	3.1	40 (control, 20)	98	82	Patient symptom free and taking part in full activities 7 mo. after operation, slight edema of thigh
								5.5	1.7	3.9		67	48	
3	44	M	2 quarts of whisky	Many	3½	++++	14.8	6.9	1.9	5.0	40 (control, 24)	—	—	Death 6 days after operation from peritonitis, gastrointestinal hemorrhage and advanced cirrhosis
4	38	M	15-20 bottles of beer	15–20	8	++++	—	5.2	1.8	3.4	21 (control, 20)	—	53	Patient symptom free, except for slight edema, and taking part in full activities 5 mo. after operation
								5.4	2.9	2.5	23 (control, 24)			
5	48	F	None	—	5	++++	2.9	6.0	1.3	4.7	26 (control, 22)	40	23	Patient convalescing and symptom free; taking part in restricted activity.
6‡	68	F	—	—	—	—	—	—	—	—	—	—	—	Poor healing of wound initially; patient doing well, except for troublesome edema, 2 mo. after operation.

*Two milligrams of bromsulfalein per kilogram of body weight injected intravenously.
†After operation.
‡This patient had chronic constrictive pericarditis.

except Case 3, in which the test was not done because of the obviously severe hepatic insufficiency.

The results may be considered good in all cases except Case 3, in which the operation was performed, despite a severe hepatic insufficiency, because of constant rapid accumulation of ascitic fluid. This patient was confused and deeply jaundiced, and showed the fetor hepaticus of cholemia throughout the hospital course. Autopsy revealed peritonitis and a stomach and upper bowel full of blood from a ruptured esophageal varix, in addition to advanced cirrhosis. A fatal outcome could have been predicted even without the button insertion and the peritonitis, which was obviously directly attributable to the button.

Other therapy that these patients received, of course, cannot be disregarded. This consisted of a high-protein, high-carbohydrate, low-fat diet, as well as 50 gm. of brewer's yeast daily, 3 gm. of choline chloride a day and, in most cases, vitamins A, B and D. Diuretics were given and preoperative abdominal paracenteses were performed as needed. The patient in Case 1 also received large amounts of plasma before operation.

Because it might be argued that these patients were cured of ascites by nonspecific measures — in other words, by the intensive medical therapy directed toward the underlying disease — Case 6 is of particular interest. This patient had chronic constrictive pericarditis. She was first admitted to the Joseph H. Pratt Diagnostic Hospital in 1940, when the diagnosis was established. Pericardiectomy was contraindicated because of severe underlying myocardial damage. Ascitic fluid, which had continuously accumulated for over six years, required repeated paracenteses, despite fluid and sodium restriction as well as the use of diuretics. The therapeutic regimen was altered only in that a button was inserted, despite the fact that a mechanically impaired heart and a high venous pressure rendered mobilization of the consequent edema difficult if not impossible. Since paracenteses were becoming necessary in increasing frequency and the potential absorptive surface is greater for edema than for ascites a trial of the button seemed warranted in this case. On a continued regimen of restricted salt and fluid the patient remained relatively free of symptoms after the insertion of the button. The edema of the lower abdominal wall and thighs continued to be troublesome. As anticipated the edema fluid was mobilized with difficulty, and mercurial diuretics were therefore frequently required. The patient was able to carry on restricted activities, however, and felt well. Adequate function of the button may be assumed from the absence of ascites, as well as the constant accumulation of edema.

It is too early to arrive at any final evaluation of the results. Bearing in mind that the only purpose of the abdominal button is the relief of ascites, it may be said that in this respect it is successful. Adequate function of the button was assured in Cases 2, 4, 5 and 6 by continuous slight edema of the lower abdominal wall and thighs, as well as by the absence of ascites. It is possible that in Case 1 ascitic fluid simply stopped forming as a result of medical therapy. Other users of a button have occasionally found that the omentum became impacted in the core and thus prevented adequate functioning of the button. This complication did not occur in any of the present series, possibly owing to the addition of the top plate. The one patient (Case 1) who was readmitted for follow-up studies showed clinical recovery. Patek's[17] criteria for clinical recovery are: weight gain and strength for full activity, disappearance of ascites, edema and jaundice, and return to normal of laboratory findings. Preliminary reports indicate that all the cases of cirrhosis, except Case 3, fulfill such criteria. The patient in Case 6, of course, benefited only in that the ascites was converted to edema, which is perhaps more easily dealt with.

Summary

The literature concerning previous attempts at surgical treatment of ascites is reviewed. A method for the treatment of ascites is presented. This consists of a glass button inserted into the lower rectus sheath so that ascitic fluid may drain from the peritoneal cavity into the subcutaneous tissues and be absorbed as edema fluid.

Five cases of Laennec's cirrhosis of the liver and 1 of chronic constrictive pericarditis are presented, in all of which the ascites was treated by the insertion of the button. The rationale for the use of the button is purely to obviate repeated abdominal paracenteses. Its main advantage over previous surgical measures for the relief of ascites is its simplicity of application. An additional value is that it returns to the patient his own ascitic fluid together with its protein content as a constant slow clysis so long as the fluid is formed.

References

1. Drummond, D., and Morison, R. Case of ascites due to cirrhosis of liver cured by operation. *Brit. M. J.* 2:728, 1896.
2. Talma, S. Chirurgische Öffnung neuer Seitenbahnen für das Blut der Vena porta. *Berl. klin. Wchnschr.* 35:833-836, 1898.
3. Monprofit, A. Traitement chirurigical de la cirrhose du foie. *Presse méd.* 12:667-670, 1904.
4. Noetzel, W. Zur Talma-Operation der Leberzirrhose. *Arch. f. klin. Chir.* 112:153-156, 1919.
5. Mayo, W. J. Surgical treatment of hepatic cirrhosis. *Ann. Surg.* 80:419-424, 1924.
6. Hughson, W. Portal cirrhosis with ascites and its surgical treatment: review of twenty-six cases. *Arch. Surg.* 15:418-440, 1927.
7. Grinnell, R. S. Omentopexy in portal cirrhosis of liver with ascites: review of twenty-three cases. *Ann. Surg.* 101:891-901, 1935.
8. Cates, H. B. Surgical treatment of cirrhosis: prognosis subsequent to omentopexy. *Arch. Int. Med.* 71:183-205, 1943.
9. Ferguson, C. Ascites: operation for its relief: case report. *J. Urol.* 50:164-168, 1943.
10. Blakemore, A. H., and Lord, J. W. Jr. Technic of using vitallium tubes in establishing portacaval shunts for portal hypertension. *Ann. Surg.* 122:476-489, 1945.
11. Whipple, A. O. Problem of portal hypertension in relation to hepatosplenopathies. *Ann. Surg.* 122: 449-475, 1945.
12. Rickles, J. Personal communication.
13. Donath, D. Personal communication.
14. Tannahill, T. Operative treatment of ascites. *Brit. M. J.* 1:281, 1930.
15. Lichtman, S. S. *Diseases of the Liver, Gallbladder and Bile Ducts.* 906 pp. Philadelphia: Lea and Febiger, 1942.
16. Ralli, E. P., Robson, J. S., Clarke, D. H., and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of liver. *J. Clin. Investigation* 24:316-325, 1945.
17. Patek, A. J., Jr. Dietary treatment of Laennec's cirrhosis with special reference to early stages of disease. *Bull. N. Y. Acad. Med.* 19: 498-506, 1943.

TUBERCULOSIS OF THE GENITOURINARY TRACT AMONG SOLDIERS IN WORLD WAR II*

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IN World War II, in the United States Army, all patients with tuberculosis — whether pulmonary or otherwise — were sent either to Fitzsimons General Hospital, Denver, Colorado, or to Bruns General Hospital, Santa Fe, New Mexico. Of the two hospitals the former was considered the senior and more important, since it was older and larger and was a permanent installation. The treatment of tuberculous patients at Fitzsimons General Hospital was typical of that in the majority of cases in the Army, and as chief of the Section of Urology from January to December, 1945, I had the opportunity to observe and treat a good deal of the tuberculosis of the genitourinary tract that occurred in the Army during that period.

The incidence of pulmonary tuberculosis was 0.9 per 1000 soldiers per year before the taking of chest x-ray films prior to separation, but increased to 1.2 per 1000 after these films had been taken. On the basis of the patient population at this hospital, the ratio of occurrence of pulmonary to genitourinary tuberculosis was approximately 33:1 — a yearly incidence of genitourinary tuberculosis of about 0.03 per 1000 soldiers.

Many different races were represented, including the White, Jewish, Negro, American Indian, Mexican, Filipino, Chinese and Eskimo. Seventeen per cent of the patients were Negroes, and there were an appreciable number of American Indians. In view of the higher percentages of these races among the tuberculosis patients than in the Army as a whole, it seems fair to conclude that they are more susceptible than the average soldiers. More than a third of the patients (38 per cent) were from the Army Air Forces, including some flying and some ground personnel. More than half the patients had been overseas, usually for a good many months, in various areas, England, Europe, the Mediterranean, the Pacific, India and Alaska, — and there was no obvious predominance of patients with tuberculosis from any one theater. Most of the patients were not in the youngest Army age group but were a little older, the average age being twenty-eight and a half years. Practically none of them gave a history suggestive of previous tuberculosis, which of course is natural in view of the fact that men with a known history of tuberculosis are not taken into the Army. Also, surprisingly few patients gave a history of tuberculosis in the immediate family or of known exposure to it.

The tuberculosis of the genitourinary tract seen in the soldiers consisted almost entirely of either renal tuberculosis or tuberculosis of the epididymis, the latter being observed in a ratio of 4:3. Both renal and epididymal tuberculosis, however, frequently occurred in the same soldier; 40 per cent of the renal cases also had tuberculosis of the epididymis, and 30 per cent of the epididymal cases had concomitant renal tuberculosis. The fact that unexpectedly few patients — only about 20 per cent of the total — had demonstrable evidence of either active or inactive pulmonary tuberculosis was quite surprising if one believes in Louis's law: "tuberculosis of any part is attended by tuberculosis of the lungs," and that the original focus for tuberculosis of the genitourinary tract is in the lungs. When pulmonary tuberculosis was found, it was more frequently associated with renal tuberculosis than with epididymal tuberculosis, since it occurred in more than a quarter (28 per cent) of the cases of renal tuberculosis and in 1 in 8 (13 per cent) of epididymal tuberculosis. Extrapulmonary manifestations of active tuberculosis did not usually coexist with genitourinary tuberculosis, but when such an association did occur the most frequent concomitant was bone and joint tuberculosis. Also found occasionally were psoas abscess, tuberculosis of cervical lymph nodes, ophthalmic tuberculosis and tuberculosis of the skin.

In almost all patients the renal tuberculosis was discovered in an early stage, — before it had become advanced, — and the lesions characteristic of advanced renal tuberculosis, such as extensive destruction of the kidney, dilated thickened and tortuous ureters, and severe inflammation and ulceration of the bladder, were not observed.

The first symptoms of renal tuberculosis were as a rule mild and occasionally entirely absent, the disease being detected only as a result of a search for the cause of a persistent pyuria. Symptoms usually consisted of mild discomfort in the back — sometimes accompanied by fever — or of somewhat increased urinary frequency. There were few cases in which bladder symptoms were prominent, and cystoscopy rarely showed the bladder to be involved to any appreciable degree. Microscopic pathological examination, however, showed the ureter to be involved to some extent in many of the cases of renal tuberculosis, except the extremely early ones.

In an appreciable number of cases the pyelogram gave evidence that was inconclusive and was suggestive of only cicatricial changes, and in a few cases the pyelograms, both intravenous and retrograde, were not abnormal and gave no help. It was found that retrograde pyelograms gave a better and more

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dependable filling and delineation of the kidney than intravenous urograms. On various occasions, when the intravenous urograms gave a picture that was either inconclusive or only faintly suggestive, the retrograde pyelogram delineated the kidney much more clearly and completely and sometimes indicated some unsuspected lesion, such as a cavity communicating with a calyx. Therefore, in any case in which the intravenous pyelogram was not quite satisfactory, clear or conclusive, retrograde pyelograms were done. In cases in which both intravenous and retrograde pyelograms were inconclusive it was necessary to depend largely on cultures of the urine, which were found to be absolutely reliable.* In no case did a kidney that had given a positive culture for tuberculosis fail to show the disease on pathological examination after removal, even though the pyelogram had appeared normal. The routine was to culture ureteral specimens of urine from each kidney and also four twenty-four-hour specimens of bladder urine, which were taken simply as a check on the kidney cultures. No case with a positive kidney culture gave negative cultures on the twenty-four-hour urine specimens; if such an event had occurred all cultures would have been repeated. If the results of the cultures did not seem in accordance with the pyelograms, or if there was a question whether or not the supposedly normal kidney was infected, the cultures were repeated before any operation, and in no case was nephrectomy performed until the healthy kidney had been shown to give a negative culture. In comparing the cultures with the stained smears of the urine, it was found that the former were much more accurate. In most cases in which the kidney urine gave a positive culture, which was later corroborated by the finding of tuberculosis in the removed kidney, the stained smears from that kidney were reported negative for tubercle bacilli. Many more positive smears were found in concentrated twenty-four-hour specimens of urine than in kidney specimens obtained at cystoscopy from the same patient, presumably owing to the greater total number of tubercle bacilli. Of course, it is true that the persistence of the person who examines the stained smear and the time at his disposal to examine the slide naturally make a great difference regarding whether or not acid-fast bacilli are found, but the cultures were nevertheless more accurate and sensitive than the smears in detecting tubercle bacilli. When the smears were positive, the cultures were almost always also positive. In a few twenty-four-hour urine specimens with positive smears, however, the cultures were negative, but after repeated smears and cultures the conclusion was reached that the acid-fast bacilli seen on the slide were contaminants, probably smegma bacilli that were indistinguishable on stain. This was another fact suggesting that the culture was more accurate and reliable than the smear. No guinea-pig inoculations were used at Fitzsimons General Hospital, although they were often used at other Army hospitals and seemed to produce reliable results. Cultures are quite reliable and have the advantage over guinea-pig inoculations in that they are less expensive and much less space is occupied.

Since cultures took two months for completion and occasionally had to be repeated, many patients spent a considerable time in the hospital before operation, but definite knowledge of the status of both kidneys was regarded as absolutely imperative before operation. Also, in view of the facts that tuberculosis is a constitutional disease and that the lesions in the genitourinary tract are secondary to tuberculosis elsewhere in the body, a careful search was made for other foci of infection. Furthermore, in agreement with other workers in this field, it was believed that a sufficiently long, unhurried period of rest and hospitalization both before and after operation improved the patient's general condition and resistance to tuberculosis, so that the results in general were improved, the patients tolerated surgery better, wound healing was better with less tendency to formation of chronic draining sinuses, and surgery was less apt to spread the disease. Unless the disease in the kidney or elsewhere, such as in the lungs, was active enough to make bed rest mandatory, the soldiers were usually not kept on strict bed rest but were allowed to be up some of the time and to partake in restricted activity.

In common with the vast majority of those who have had the opportunity to observe renal tuberculosis, it was believed that the normal kidney does not filter tubercle bacilli from the blood stream to the urine, that tubercle bacilli in the kidney urine obtained by ureteral catheterization denote renal tuberculosis, and that any renal lesion that has progressed so far as any degree of ulceration will not heal spontaneously but will tend to progress despite sanatorium care. Therefore, when the diagnosis of tuberculosis of one kidney had been made and the other kidney was free of disease, nephrectomy was carried out, unless it was contradicated by some complication in the patient's condition. Bilateral renal tuberculosis was exceedingly rare, and was always found in association with active tuberculosis elsewhere in the body. Nephrectomy was not performed in any case of bilateral tuberculosis. If a case of bilateral disease is encountered, however, in which one kidney is badly diseased and destroyed and the other has only a minimal trace of the disease, it is my opinion that nephrectomy of the badly damaged kidney may be advisable. In such a case it is well known that nothing can stop the badly damaged kidney from continuing to deteriorate, and its removal may ameliorate or prevent the development of an excruciatingly painful tuberculous

*The culture medium used was Petragnani's medium, whose chief constituents are potatoes, milk and eggs.

cystitis and also removes a tuberculous focus from the body. If active pulmonary tuberculosis existed, nephrectomy was not done until the process in the lung was arrested or quiescent to a point where operation was no longer contraindicated. In fact, in such cases, operation was considered desirable to remove a tuberculous focus from the body.

The type of operation done was the ordinary lumbar nephrectomy. The healing was so satisfactory in practically all cases that there seemed to be no object in doing a nephroureterectomy, especially since this procedure would have entailed another incision and put the patient through a more serious operation, increasing the likelihood of morbidity and mortality. In most cases the ureter was simply ligated, carbolized and dropped back into the wound. In some cases in which the ureter was dilated, thickened, tortuous and obviously diseased, it seemed better insurance against chronic sinus formation in the nephrectomy wound to bring the upper end of the remaining ureter out through a tiny stab wound below the main wound. In these soldiers as a group, however, the renal tuberculosis was discovered in an early stage and there were comparatively few of the dilated, thickened and tortuous ureters seen in advanced renal tuberculosis. The wounds were drained with soft rubber drains for twenty-four to forty-eight hours to let out serum, after which the drains were removed, because it was believed that leaving them in might help create a chronic sinus. Most of the nephrectomies were done under spinal anesthesia, which had the advantage that the patients could start taking frequent deep-breathing exercises immediately after operation as a prophylaxis against such pulmonary complications as atelectasis. For the same reason, the patients were made to lie with the operated side down for much of the time for the first twenty-four hours. If the spinal anesthesia wore off during the operation, it was supplemented with a small amount of Pentothal Sodium intravenously. To avoid thrombophlebitis, the patients were allowed out of bed beginning the day after operation; in fact, they occasionally stood up beside the bed on the evening of the operation, to try to void in a more natural position. Despite the fact that the patients continued to get out of bed every day beginning the day after operation, no weak or bulging scars resulted. No wounds broke down, although in 1 case much of the skin incision broke open. There were several cases in which a small draining sinus persisted for weeks. Almost to a man the patients withstood nephrectomy well, and there were no postoperative deaths in the twelve months ending in December, 1945.

Tuberculosis of the epididymis was the most frequent form of genitourinary tuberculosis encountered — 68 per cent of the total. This condition was bilateral in slightly more than a quarter (28 per cent) of the cases and unilateral in the rest. In the cases of epididymal tuberculosis renal tuberculosis was also present in 30 per cent and pulmonary tuberculosis in 13 per cent.

The first symptom of epididymal tuberculosis noticed by the soldiers was usually a somewhat painful swelling in the affected scrotum that came on gradually over a period of weeks or months. Sometimes pain was absent, whereas the pain and swelling occasionally developed rapidly in the course of a few weeks or even a few days. Most soldiers noticed this condition themselves, but in rare cases it was discovered during a routine general physical examination. The diagnosis was made largely on the basis of the physical examination, which characteristically revealed the whole epididymis to be greatly enlarged, hard, nodular and irregular, but not extremely tender. When only the lower pole was grossly diseased there was a typical hard mass at the lower pole in the shape of a large, thick, irregular button. This was practically always adherent to the skin of the scrotum, which was by far the most frequent site for a draining sinus. In a few cases the tuberculous process had definitely spread from the epididymis to involve the testis. The vas deferens was involved in most cases, and was frequently thickened and occasionally beaded. The seminal vesicle on the diseased side and also the prostate often had indurated, irregular and nodular areas — evidence that they were also involved in the pathologic process. In more than a third of the cases (37 per cent) a draining sinus had become established before hospitalization, usually after spontaneous rupture of a scrotal abscess but occasionally following surgical drainage of an abscess. In all cases in which sinuses had once become established spontaneous healing did not take place, and although the sinuses sometimes healed temporarily, they continued to drain until the diseased epididymis — as well as the testis, when it was involved — was finally removed surgically. For this reason, and also to remove foci of tuberculous infection in the body, operation was performed in all these cases.

The technic used was as follows. If a draining sinus existed, a panel of skin was cut so as to surround the sinus with a good margin, and this incision was deepened down to the epididymis so that the panel of skin containing the sinus came away en bloc when the epididymis was removed. The same procedure was frequently followed when the epididymis was adherent to an area of the scrotal skin, the adherent skin being removed with the epididymis. When the scrotal cavity had been entered the vas deferens was isolated near the epididymis, sectioned with a knife and treated with carbolic acid. The upper end of the vas was freed from the rest of the cord up to the external inguinal ring and then brought out without tension through a tiny stab wound about 2.5 cm. lateral to the base of the penis, where it was fixed with a stitch so that about 1 cm. projected beyond the skin, any excess of vas being resected. The lower part of the vas and

the whole epididymis were then dissected en bloc from the testis. As a rule the epididymis was not too adherent at the upper pole of the testis, and it was usually not difficult to dissect it free without damaging the main blood supply of the testis, which enters near the upper pole. At the lower pole, however, the epididymis was apt to be extremely adherent, so that sharp-knife dissection was almost always necessary to separate it from the testis. Frequently abscesses were broken into during the dissection, but this gross contamination of the wound with tubercular pus did not appear to affect the healing adversely. The scrotum was always drained with a soft-rubber wick, to release oozing blood and serum, but this wick was always removed at the end of forty-eight hours, to avoid the creation of chronic sinus in the presence of a disease that is notorious for its tendency to sinus formation. In general these wounds healed satisfactorily, and in no case did the scrotal incision break down. But in the great majority of cases drainage via the wick hole persisted for at least two weeks, and occasionally longer, although in a few cases there was no significant drainage and the wounds healed completely in a few days. In cases in which the drainage tended to persist, heliotherapy was used, which was regarded as a definite aid in the healing process. The projecting exteriorized end of the vas gradually melted back to the level of the skin, and when drainage ceased it healed over. As might have been expected, the vasa most prone to drain were greatly thickened, contained pus in the lumen and were obviously markedly involved by tuberculosis. The drainage lasted all the way from several days to several months, but the average time was ten to fourteen days and in some cases there was little drainage. As in the nephrectomy cases all patients started getting out of bed the day after operation.

Bringing the vas out on the skin through a tiny stab wound is important. Since most of the vasa and many of the seminal vesicles with which they connect are tuberculous, they usually drain moderately. Exteriorizing the end of the vas allows the drainage to discharge on the skin, where it can be taken care of easily and where it can do no harm. Several cases were seen in which epididymectomy for tuberculosis had been performed elsewhere but the upper end of the vas had been allowed to remain inside the scrotum, and in which either a scrotal abscess or a chronic draining sinus in the scrotum had formed, both of which complications could have been avoided by exteriorizing the draining upper end of the vas at the time of operation. In this group of cases there were no deaths following epididymectomy or epididymo-orchidectomy.

Summary

The incidence of pulmonary to genitourinary tuberculosis among soldiers in the Army seen at Fitzsimons General Hospital in 1945 was approximately 33:1. Negroes and American Indians had a high incidence.

Two main forms seen were renal tuberculosis and tuberculosis of the epididymis, the latter being more frequent in a ratio of 4:3. Both forms occurred in about a third of the cases.

Only about 20 per cent of the soldiers with genitourinary tuberculosis had demonstrable pulmonary tuberculosis, which was found twice as often in association with renal as with epididymal tuberculosis.

In these soldiers, since the renal tuberculosis was discovered in an early stage, the first symptoms were mild — backache, some frequency and symptomless pyuria.

Retrograde pyelograms were more reliable and informative than intravenous pyelograms, but often all pyelograms were inconclusive and cultures had to be depended on to make the diagnosis of tuberculosis.

Nephrectomy was the treatment for unilateral renal tuberculosis. Soldiers withstood operation well, wound healing was good, and there were no deaths.

Epididymal tuberculosis was bilateral in a quarter of the cases. Scrotal abscess that had ruptured spontaneously, followed by persistently draining sinuses had occurred in more than a third of cases before hospitalization. First symptom was usually gradual, slightly painful swelling of the epididymis, which became large, hard and irregular. Epididymectomy, preserving the blood supply of the testis, was the treatment of choice. The wounds healed well, and there was no mortality. Exteriorizing the upper end of the vas deferens on the skin, so that it can drain there rather than inside the scrotum, is of real value.

The value of a prolonged period of hospital rest both before and after surgery cannot be overestimated. This results in improvement in the patient's general condition and resistance to tuberculosis, so that surgery is better tolerated and is less apt to spread the disease, and wound healing is better, with less tendency for chronic draining sinuses to develop.

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MEDICAL PROGRESS

ACUTE PULMONARY EDEMA, WITH SPECIAL REFERENCE TO EXPERIMENTAL STUDIES*

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BALTIMORE

THERE are many discrepancies between clinical observations, modes of therapy and the conventional explanations of the pathogenesis of pulmonary edema. Even superficial consideration reveals the inadequacies of the accepted explanations for this striking syndrome. In 1941 an editorial called attention to this problem, as follows: "Unfortunately as experimental and clinical observations on pulmonary oedema have accumulated it has become clear that the validity of the 'back pressure' or 'left ventricular failure' theory can no longer be considered as established."[1]

DEFINITION

Acute pulmonary edema is a syndrome characterized by rapid flooding of the lung alveoli with a serous or serosanguinous fluid; it occurs in a great variety of clinical states, and may rapidly jeopardize the life of the patient.

Its nonspecific name has led to confusion with cardiac asthma, paroxysmal dyspnea or paroxysmal nocturnal dyspnea and chronic pulmonary edema. Cardiac asthma is constantly associated with heart disease; ancillary signs of congestive failure and asthmatic wheezes throughout the chest are usually present. Paroxysmal dyspnea, a closely related symptom of pulmonary congestion found in heart disease, usually appears at night and seems to be the same as cardiac asthma except for the associated bronchial constriction. Chronic pulmonary edema is found in congestive heart failure; pericapillary edema is rather constant, and the condition is rarely characterized by the explosive onset often found in acute pulmonary edema. The hyperneic phases of periodic breathing or Cheyne–Stokes respiration are easily differentiated from the syndrome under consideration; the former's name discloses the differential point involved. In spite of this apparently easy differential diagnosis, acute pulmonary edema is frequently confused both in the literature and clinically, and often must appear in its full-blown state before proper therapy is instituted on the basis of exact diagnosis.

INCIDENCE

Luisada[2] has reviewed the literature of acute pulmonary edema. There is no satisfactory report on the incidence, and since patients often do not die primarily from this condition, even hospital statistics are not entirely relevant. Such figures are greatly needed, however. It is to be hoped that material from both adult and children's hospitals will be included in such a review, since heart disease is far less frequent in the latter.

Reid and Teel[3] state that pulmonary edema is a frequent immediate cause of death in cases of nonconvulsive toxemia. Nessa and Rigler,[4] in 1941, collected a series of 110 post-mortem cases of pulmonary edema in which the average age was fifty-seven years, with a variation from three months to eighty years. The primary cause of death was carcinoma in 17 cases (16 per cent); vascular accident in 20 (18 per cent); renal disturbance in 8 (7 per cent); cirrhosis and acute degeneration of the liver in 5 (5 per cent); blood dyscrasias in 4 (4 per cent); burns in 4 (4 per cent); septicemia in 4 (4 per cent); miscellaneous in 22 (20 per cent); and various surgical procedures in 26 (24 per cent). The high percentage of surgical deaths is particularly notable in this series. Farber[5] states that acute pulmonary edema is one of the most frequent causes of death found at autopsy in infants and children.

DESCRIPTION OF THE ATTACK

An excellent clinical description has been provided by Sir Thomas Lewis,[6] as follows:

> The onset may resemble exactly that of the attacks previously described, occurring usually at night and waking the patient from sleep; or it may come in the hours of daylight and wakefulness. The separation of these attacks from those previously described [cardiac asthma] is in fact arbitrary and necessitated only by the relative dryness of the latter and their frequent repetition. In frank pulmonary oedema, while breathlessness is usually urgent from the start, cough is more prominent, and frothy blood-stained fluid is freely or profusely expectorated. The march of events is often speedy. Cyanosis deepens rapidly; breathing becomes progressively more urgent and less effective. The attack may last at its height for hours. In fatal attacks the pulse becomes steadily weaker until imperceptible, the veins swell, and breathing becomes more gasping, less frequent, and then weaker until it ends.
>
> In a fulminating form, the oedema occurs so rapidly and is so intense that, within a minute or two of crying out in fear, the patient is drowned by the copious blood-stained fluid that pours into the respiratory passages and overflows frothing from the mouth and nose.

ROENTGENOLOGIC FINDINGS

Nessa and Rigler,[4] in a discussion of the x-ray picture, refer to the classic butterfly-shaped, fairly

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symmetrical density of both lungs that is greatest at the hilus and gradually fades out toward the periphery; the apexes and extreme bases are usually clear. The density is homogeneous and obliterates all structural detail in the lung. The fluid collects in groups of alveoli, resulting in an irregular stippled density on the roentgenogram. The edema is often predominantly on one side or entirely unilateral. The condition is distinguished from pulmonary congestion by the presence of enlarged hilar shadows and dilated vessels throughout the lung fields and is further distinguished from massive atelectasis by elevation of the diaphragm, shift of the mediastinum and collapse of the chest wall. Lateral films revealed the congestion and edema to be central and not peripheral, in contrast to the congestion in pneumonia, which is usually peripheral in onset.

Pathology

Farber[7] and Moon[8] described the pathology of pulmonary edema, the former observing the same pathological findings in rabbits following cervical vagotomy. There were massive pulmonary edema, often with bloody fluid, and slight dilatation of the right ventricle and auricle. Pulmonary edema was present in the air and interstitial spaces; the former showed albuminoid casts and linings. The veins, capillaries and lymphatics were tremendously dilated, and the arterioles moderately so. Under direct vision in his experiments, Farber saw first the appearance of red petechiae of consolidation on the surface of the lung, with later enlargement and terminal dilatation of the right side of the heart. These changes in the heart, which have long been a source of controversy, are often explained as a result rather than a cause of the pulmonary edema. Undoubtedly, with such massive edema, obstruction to the flow of blood follows, pulmonary arterial pressure rises,[9] and dilatation results, for the right side of the heart is working against a greater bed of fluid. Similarly, if a great amount of fluid is rapidly lost into the lungs, one might expect decreased return to the left side of the heart, with consequent decrease in size. Earlier workers sought to explain the dilatation frequently seen by failure of the right side, but it is difficult to understand how such failure could cause congestion of the lungs.

The fluid of pulmonary edema is usually characterized as a plasma filtrate with a high concentration of protein. Blood is found in varying amounts. Renaut and de Basch[10] demonstrated the absence of fibrin and inability to clot in pulmonary edema fluid. Peserico[11] reported a vasodilatory effect that he believed to be due to the presence of histamine in large quantities.

Pathologic Physiology

Several features of the pathologic physiology of acute pulmonary edema are worthy of note.

Vicious circle of anoxia. It is an old maxim that anoxia begets anoxia, and this is especially true of the lungs, for with the onset of anoxia there is increased capillary permeability and resultant pulmonary edema. In turn this edema prevents aeration of the alveoli and oxygenation of the blood, promoting and advancing the anoxia and edema. Drinker[12] presents many graphic illustrations of the drastic effect of anoxia on the lung capillaries and comments on their special susceptibility.

Ineffectual drainage. Drinker[12] refers to the inadequacy of lymphatic drainage to clear pulmonary exudates and transudates. He points out three routes of removal: the bronchi and trachea, reabsorption and enzymatic digestion and resorption of the smaller molecular compounds.

Rise in venous pressure. Many authors mention a rise in venous pressure with attacks of acute pulmonary edema, accepting this as evidence of a failing heart, with so-called "back pressure," and tacitly regarding cardiac failure in an acute and unusual form as the cause of acute pulmonary edema. Schmidt[13] reports that positive intrathoracic pressures as high as 100 mm. of mercury may be obtained during forced expiration, such as that in asthmatic breathing. Such a heightened pressure impedes venous return from the head, leading to dilated neck veins. With the respiratory obstruction of massive edema, dilated neck veins may well represent no more than a heightened intrathoracic pressure during expiration.

Blood-pressure changes. Frugoni[14] summarized the literature in 1931 and concluded there was no characteristic change in blood pressure with these attacks. Pulmonary edema of itself may well introduce changes in arterial tension. Schweigk[15] and Parin[16] demonstrated a reflex lowering of systemic arterial pressure, with an increase in pulmonary-artery pressure, that might explain some of the changes seen. Asphyxiation causes first a rise and later a fall in blood pressure, and many of the patients are certainly suffering from asphyxiation. Fishberg[17] states there is a primary fall in blood pressure, followed by a rise, with anoxia. Lambert and Gremels,[9] in Starling's Laboratory, noted in their experiments on heart-lung preparations that the pulmonary pressure in edema rose to high levels in the absence of cardiac failure.

Dyspnea. Since dyspnea is such a prominent part of acute pulmonary edema and related conditions it is advantageous to review this subject by means of Altschule's[18] schematic chart of some of the factors producing dyspnea in congestive failure (Fig. 1). It will be noted that most of the factors here involved are also involved in acute pulmonary edema.

General circulatory changes. Subsequent to the onset of pulmonary edema there is a loss of a great quantity of fluid into the lungs, with resultant depletion of the circulating blood volume. The small, rapid, thready pulses noted by clinicians in

the late stages may well represent the onset of true shock. A rise in the hematocrit is frequently seen and is also due to loss of plasma into the alveoli.

Heart-lung preparations. Many investigators have observed pulmonary edema in heart-lung preparations but have attached varying significance to the factors involved. Modrakowski,[19] Matsuoka[20] and others emphasized the critical levels of the pulmonary arterial or general venous pressures necessary for the appearance of the pulmonary edema. Lambert and Gremels[9] and Wiggers[21] considered such pressures to be beyond the physiologic range. Lambert and Gremels[9] and Newton[22] observed that such preparations caused degenerative changes in anoxemia of pulmonary edema, however, there may be increased venous return and increased cardiac output.[25] It is well known that a decreased velocity of peripheral and pulmonary blood flow occurs in patients with congestive failure,[26] but systematic investigations of the cardiac output by the newer methods and circulation times in patients with pulmonary edema have not been performed, probably owing to the serious nature of the paroxysms.

The urine. There are many references in foreign reports to abnormalities of the urine following attacks of pulmonary edema. Some authors have even claimed that the albuminuria often noted is due

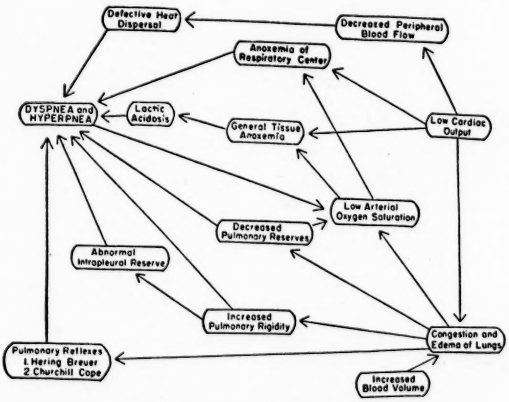

FIGURE 1. *Factors in the Dyspnea of Chronic Cardiac Decompensation (Altschule[18]).*

the intima of the lung capillaries, the edema being attributed principally to injury to the capillary endothelium and the greater permeability thereby produced. The toxic action of old defibrinated blood used in heart-lung circulations is well known. Thus the place of such preparations in pulmonary edema remains uncertain.

Cardiac output and circulation time. Harrison,[23] in a review of the studies on cardiac output in cardiac asthma and acute pulmonary edema, states the following: "The idea that cardiac asthma is precipitated by increase in the cardiac output (due to decreased sympathetic activity during sleep, decreased peripheral resistance and hence increased venous return) has not been supported by recent work." In fact, the peripheral circulation has been found to be essentially normal, with no constant changes in cardiac output.[24] With the onset of the

to the resorption of albumin from the alveoli after the attack. Frugoni[14] studied this problem and came to the conclusion that any urinary abnormalities merely reflected the underlying disease and were not characteristic of or caused by the attack of acute pulmonary edema.

ETIOLOGY

In the literature no lengthy studies on the incidence of pulmonary edema have been reported, and it is only recently that cases of obviously neurogenic origin have attracted the attention of English and American observers. Cases of cardiovascular disease appear to be predominant, but there are probably more cases of obviously neurogenic origin than has heretofore been appreciated. The variety of cases alone should throw some doubt on a mechanical or cardiac origin of this syndrome.

Cardiovascular diseases. Types of cardiovascular diseases presenting this syndrome are as follows: aortic regurgitation and aortitis[2, 27–30]; angina pectoris[30]; coronary thrombosis[27, 30]; pericarditis[29, 30]; mitral stenosis[29–31]; cardiac failure[17, 31]; hypertension[30]; wounds of the heart[29]; and cardiac aneurysm.[29]

Toxic gases.[30, 32, 33] Carlisle[33] gives the following list of the industrial gases that cause pulmonary edema: oxides of nitrogen, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, methyl bromide, chlorine, cadmium and dust from certain alkaloids.

Drowning.[30, 34] Luisada[34] mentions drowning or the penetration of sea water into the upper respiratory passages as a cause of pulmonary edema. It is interesting to note that the lungs of drowning people do not contain sea water but rather the albuminous plasmalike fluid found in other cases of pulmonary edema.

Uremia.[17, 27, 29, 30, 35, 36] Teisser[29] remarks on the frequency of acute pulmonary edema with nephritis and nephrosclerosis and the rarity of the syndrome in pure epithelial nephritis. He mentions gout as another cause, and regards the degree of renal insufficiency as determining the severity of the attack of pulmonary edema. Fishberg[17] believes that the pulmonary edema of renal disease is due to accompanying cardiac weakness.

Pregnancy and toxemia of pregnancy.[2, 27, 30, 35] Reimann[30] noted the incidence of pulmonary edema during pregnancy and considered it more frequent in pregnant women than in those with primary cardiac conditions. Reid and Teel,[8] who studied this problem extensively, remarked that pulmonary edema is often an immediate cause of death from nonconvulsive toxemia. Among other measures they recommend rapid emptying of the uterus as part of the therapy.

Paracentesis.[14, 29, 30, 37, 38] Edema has been described following thoracic or abdominal paracentesis. In 1943, Vidal, Fourcade and Girard[38] reported that contralateral pulmonary edema was provoked by the creation of an extrapleural pneumothorax.

Central-nervous-system damage or disease.[27, 31] The following conditions are cited as causes of pulmonary edema: intracranial hemorrhage[24, 27, 39]; insulin hypoglycemic coma[40, 41]; brain tumor[39]; head wounds and trauma[30, 34, 37, 39, 43–44]; diseases of the peripheral vagus[39, 45]; acute ascending myelitis[29, 30, 34, 37, 42]; tetanus[34]; cerebral embolism and thrombosis[30, 37]; vertebral injuries[37, 46]; encephalitis[37, 42]; polyneuritis and polyradiculitis[37]; tabes dorsalis[29, 37]; lumbar puncture[37]; phrenic-nerve crush under local anesthesia[47]; cervical sympathectomy[46, 48]; laminectomy[46]; and emotional disorders and hysteria.[29, 37] Weisman,[39] in 1939, published an interesting series of 686 cases of intracranial hemorrhage with frequent pulmonary edema. In about two thirds of the cases the combined weight of the lungs was over 900 gm., whereas in the control group only 2 per cent of cases showed lungs of this size. Severe edema and congestion of the lungs developed almost immediately after intracranial hemorrhage — that is, within thirty minutes to an hour.

Epileptic seizure. Several reports list epileptic seizure as a cause of pulmonary edema.[30, 37, 39, 49–51]

Infections.[30, 31] The following infections are regarded as initiating pulmonary edema: acute rheumatic fever[29, 52]; puerperal fever[29]; typhoid fever[29, 52]; measles[52]; scarlet fever[52]; and whooping cough.[52] The acute circulatory changes described by Freedberg and Altschule[54] in the various phases of fever may also play a part in the pulmonary edema of infections.

Toxic factors. Teisser[29] reports cases of pulmonary edema in human beings associated with alcoholism and venoms, and in animals following the ingestion of potassium iodide, iodoform, pilocarpine and after intravenous injections of muscarine, chlorine, prussic acid, amyl nitrite and methyl salicylate. Reimann[30] lists among the toxic causes alcohol, barbital, iodine, morphine, epinephrine and asphyxiating gases. Bard[55] reported cases following muscarine poisoning.

Miscellaneous causes. Newmayer,[53] in 1907, reported pulmonary edema during the exertion of coitus and following shocking news. Gibbon and Gibbon[56] produced pulmonary edema in cats by lobectomy and plasma infusions and warned of clinical repetition of this danger. Other initiating factors are allergy,[2] thyroid storm,[57] beriberi[35] and reflexes from internal organs during operations. Bookhamer and Cullen[36] reported a case following manipulation of the stomach at operation for Banti's disease. Eason and Karp[35] mention angioneurotic edema and distention of abdominal organs. Fisher[58] reported a case of pulmonary edema, with anesthesia of the entire body as well as respiratory paralysis, following spinal anesthesia using 140 mg. of Metycaine in 14 cc. of water. Moon[8] produced edema experimentally by intravenous muscarine, iodine, adrenalin in large amounts, serum in sensitized animals, perfusion of heart-lung preparations with old defibrinated blood, intravenous bile salts, in burns and intestinal obstruction. Most of these cases were observed in animals in shock. Moon[8] and Reimann[30] commented on the frequency of pulmonary edema in shock, especially when death was somewhat delayed. MacKenzie and MacKenzie[59] found that thiourea and phenyl thiourea rapidly produced pulmonary edema in rats, and Drinker[12] mentions a simple thiourea compound that caused edema regardless of the route of administration. Choisy[60] reported a case of pulmonary edema with a hypertension apparently elicited by postmenopausal injections of steroids.

Anatomy and Physiology of Heart and Lungs

Control of Pulmonary Vascular Tone

The problem of pulmonary vascular tone has been disputed for years, and although a definite formulation has not been accepted by all workers the data are quite complete. De Burgh Daly[61] stated that a complete understanding of the nervous mechanisms controlling the lung blood vessels is still lacking, but that workers who have analyzed and summarized the available data generally agree that such control exists. Olkon and Joannides,[62] in 1930, observed under the microscope caliber changes of the alveolar capillaries in dogs, as well as localized hemorrhages on stress of hyperventilation and convulsions, and attributed their findings to vasomotor control over these vessels. De Burgh Daly and von Euler[63] showed that excitation of the stellate ganglion caused pulmonary vasoconstriction, whereas stimulation of the cervical vagi and the cervical or thoracic vagosympathetic nerves produced strong vasoconstriction in some preparations but weak vasodilatation in others. The results of experiments on dogs were summarized as follows:

> In view of the finding by these workers that excitation of the thoracic vagosympathetic nerves may augment the mean effective pulmonary arterial pressure 40 per cent, a rise approximating to that obtained by occlusion of the main arterial branch to one lung, it would seem that the vasomotor nerves to the lungs may exert under certain conditions a profound effect on the pulmonary arterial pressure. If such profound changes occur normally the pulmonary vasomotor nerves may maintain a more or less constant pulmonary arterial pressure at all circulation rates, thereby preventing overloading of the right side of the heart.[61]

Adrenalin raises pulmonary arterial pressure and in general constricts pulmonary vessels, although some reports deny such constriction.[27, 61]

In general, acetyl choline causes vasodilatation of pulmonary vessels. Several workers have shown dilatation of arterioles and constriction of veins with acetyl choline.[27, 61, 64]

De Burgh Daly and von Euler[63] demonstrated in experiments with eserine and atropine that pulmonary vasoconstrictor fibers in the rabbit belonged to the parasympathetic system. Similar pharmacologic evidence was presented by Berry and De Burgh Daly[65] in support of the presence of parasympathetic vasoconstrictor fibers running in the same nerves, as well as of sympathetic vasoconstrictor and dilator fibers in the thoracic vagosympathetic nerves of dogs, since the constrictor effect following excitation was suppressed or reversed by ergotamine tartrate. Kuré and his associates[66] described vasoconstrictors of the pulmonary vessels in the dog arising from spinal parasympathetic fibers in the dorsal spinal roots.

Luisada[27] raises the question whether vasomotor tone controls permeability of the pulmonary vessels and quotes Krogh's opinion that dilatation and permeability are parallel actions. Heidenhain and Klemensieviez[67] claimed experimental proof of such direct vasomotor control of permeability.

In summary it can be said that there is vasomotor control of pulmonary vessels, probably with mixed action by both parasympathetic and orthosympathetic fibers. Adrenalin constricts the pulmonary vessels and acetyl choline dilates arterioles and constricts veins. Vasomotor control of permeability is a possibility.

Nerve Supply to Heart and Lungs

A brief review of the nervous pathways to these organs is included to demonstrate the pathways available for reflexes.

Miller[68] writes as follows:

> The lungs receive their nerve supply from two sources: the vagi and the sympathetic nerves. Each vagus nerve, on reaching the back of the root of the lung, breaks up into numerous branches which, reinforced by fine branches from the second, third, and fourth thoracic ganglia of the sympathetic system, form the pulmonary plexuses. Each plexus gives off fibers which are distributed to the bronchi and pulmonary artery at the hilum. On entering the lung these fibers form two main plexuses which are distributed, one about the main-stem bronchus and its branches, the other about the pulmonary artery and its branches.

Another description of the nervous pathways is given by Karsner.[69]

Larsell[70] concluded that the plexuses and ganglions of the human lung are in general similar to those described in the dog and rabbit. Afferent nerve endings are found in the bronchi as far as the proximal end of the alveolar ducts, in the atrial walls and in the bands of bronchial muscle, as well as in the adventitia of the pulmonary artery and the perichondrium of the bronchial cartilage plates. Terminations of motor type, which are present in the bronchial muscles and bronchial mucous glands, appear to arise from the nerve cells of the bronchial ganglions. Nerve fibers ending in the smooth muscle of the pulmonary and bronchial arteries originate from the periarterial plexus, which appears to be composed of postganglionic fibers from the upper thoracic sympathetic ganglions. Fibers from the periarterial plexus extend into the parenchyma and form a plexus of delicate nerve fibers on the pulmonary capillaries; terminal fibers end on the capillary walls.[70, 71] The vagal efferent fibers arise from the dorsal nucleus of the vagus in the medulla and pass via the vagal trunk to be distributed over both lungs, their peripheral ganglions lying over the hilus of the lung. The vagal afferent pathways are again via the vagal trunk to the nodose ganglion lying just below the jugular foramen.[27]

In 1926 Rasmussen[72] described the nervous pathways as follows:

> The sensory fibers of the vagus enter the upper portion of the medulla oblongata, where some terminate in the immediate neighborhood, while others run downward toward the spinal cord as part of the solitary fasciculus to end in various centers, especially the respiratory center. A few fibers may even go down into the spinal cord as far as the

first cervical segment (Cajal). Freeman in 1925 has also described a bundle of fine fibers as far as the third cervical segment.

The sympathetic supply to the lungs comes from the lateral horns of the spinal medulla via white rami from the second through the sixth thoracic ganglions. Most of the sympathetic fibers come through the stellate ganglion. Apparently the sympathetic supply is also distributed bilaterally to the lungs. There are also afferent pathways through these sympathetic fibers to the stellate ganglion and to the posterior horn cells of the cord via the gray rami.[27]

Kuré[66] claims to have demonstrated a spinal thoracic parasympathetic center and fibers, and although his work has not yet been confirmed[13] some of his conclusions are of interest. He states that stimulation of fibers leaving the cord by the dorsal roots causes marked constriction of the pulmonary vessels of the dog, and that the spinal parasympathetic fibers therefore have a vasoconstrictor action on the lung while acting as vasodilators on the skin and viscera generally; the spinal center of the vasoconstrictors for the lung is situated in the thoracic region from the fourth to the eighth segments.

Cardiovascular Reflexes

Farber[73] in 1940, reported that rapid intravenous infusions in rabbits produced only moderate vascular congestion but after cervical vagotomy caused acute pulmonary edema:

> Cervical vagotomy deprives the animal of the function of the nerve endings in the walls of the venae cavae and the pulmonary veins recently localized by Nonidez. The nerve endings in these locations are responsible for the acceleration of the cardiac rate induced by a rise in the pressure of blood entering the right auricle (the Bainbridge Reflex).
>
> In recent experiments in dogs, Schweigk found that branches of the pulmonary artery possess nerve endings responsible for reflex pressosensitivity. This mechanism regulates the cardiac rate and arterial vasomotor tone; an increase in the pressure within the pulmonary arterial system causes reflex slowing of the heart and vasodilatation; lowering of the pressure within the pulmonary arteries is responsible for opposite cardiovascular reactions. These reactions cannot be elicited if the nerve fibers from the pulmonary arteries which connect with the vagus nerves are severed. Schweigk expressed the belief that during periods of pulmonary congestion the reflex lowering of the general blood pressure caused by a rise in the pulmonary arterial pressure is accompanied by peripheral and splanchnic vasodilatation, which tends to prevent overloading of the pulmonary circulation. It may be suggested also that at times of temporary increase in the pressure in the pulmonary artery such a mechanism might exert a beneficial influence on the pulmonary circulation by preventing an increase in pressure in the bronchial artery.

(To be concluded)

References

1. Editorial. Acute pulmonary oedema. *Brit. M. J.* **1**:447, 1941.
2. Luisada, A. Pathogenesis of paroxysmal pulmonary edema. *Medicine* **19**:475-504, 1940.
3. Reid, D. E., and Teel, H. M. Cardiac asthma and acute pulmonary edema complicating toxemias of pregnancy: further observations. *J. A. M. A.* **113**:1628-1631, 1939.
4. Nessa, C. B., and Rigler, L. G. Roentgenological manifestations of pulmonary edema. *Radiology* **37**:35-46, 1941.
5. Farber, S. Personal communication.
6. Lewis, T. *Diseases of the Heart Described for Practitioners and Students.* Second edition. 297 pp. New York: The Macmillan Company, 1937.
7. Farber, S. Studies on pulmonary edema. *J. Exper. Med.* **66**:397-411, 1937.
8. Moon, V. H. *Shock and Related Capillary Phenomena.* 442 pp. New York: Oxford University Press, 1938.
9. Lambert, R. K., and Gremels, H. Factors concerned in production of pulmonary oedema. *J. Physiol.* **61**:98-112, 1926.
10. Renaut and de Basch. Cited by Teisser.[29]
11. Peserico. Cited by Frugoni.[14]
12. Drinker, C. K. *Pulmonary Edema and Inflammation: An analysis of processes involved in the formation and removal of pulmonary transudates and exudates.* 106 pp. Cambridge: Harvard University Press, 1945.
13. *Macleod's Physiology in Modern Medicine.* Edited by P. Bard. Ninth edition. 1256 pp. St. Louis: C. V. Mosby Company, 1941.
14. Frugoni, C. L'edema polmonare acuto. *Riforma med.* **46**:1615-1617, 1930.
15. Schweigk. Cited by Farber.[73]
16. Parin, V. V. Pulmonary hemodynamic reflexes. *Am. Rev. Soviet Med.* **1**:251-263, 1944.
17. Fishberg, A. M. *Hypertension and Nephritis.* Fourth edition. 779 pp. Philadelphia: Lea & Febiger, 1939.
18. Altschule, M. D. Pathological physiology of chronic cardiac decompensation. *Medicine* **17**:75-154, 1938.
19. Modrakowski, G. Beobachtungen an der überlebenden Säugetierlunge. *Arch. f. d. ges. Physiol.* **158**:527-554, 1914.
20. Matsuoka, Y. Contribution to pathology of obstructive oedema of lung, based on observations with Starling heart-lung preparation. *J. Path. & Bact.* **20**:53-75, 1915.
21. Wiggers, C. J. *Physiology in Health and Disease.* Fourth edition. 1174 pp. Philadelphia: Lea & Febiger, 1944.
22. Newton, W. H. Pulmonary oedema in cat heart-lung preparation. *J. Physiol.* **75**:288-304, 1932.
23. Harrison, T. R. *Failure of the Circulation.* Second edition. 502 pp. Baltimore: Williams and Wilkins, 1939.
24. Weiss, S., and Robb, G. P. Cardiac asthma (paroxysmal cardiac dyspnea and syndrome of left ventricular failure). *J. A. M. A.* **100**: 1841-1846, 1933.
25. Jones, E. Cited by Harrison.[23]
26. Blumgart, H. L. *The Velocity of Blood Flow in Health and Disease.* 75 pp. Baltimore: Williams & Wilkins Company, 1931.
27. Luisada. Cited by Frugoni.[14]
28. Williams, L. Acute pulmonary oedema. *Lancet* **2**:1606, 1907.
29. Teisser, J. De l'oedème aigu du poumon. Ct. r. 13th Congrès International de Médecins (Paris, 1900).
30. Reimann, H. A. Diseases of the lung. In: *A Textbook of Medicine.* Edited by R. L. Cecil. 1744 pp. Philadelphia: W. B. Saunders Company, 1940. Pp. 932-960.
31. White, P. D. *Heart Disease.* Third edition. 1025 pp. New York: The Macmillan Company, 1944.
32. Barach, A. L. Treatment of pulmonary edema due to gas poisoning in war and in civilian life: with special reference to use of positive-pressure respiration. *New Eng. J. Med.* **230**:216-223, 1944.
33. Carlisle, J. M. Pulmonary edema. *J. A. M. A.* **123**:947, 1943.
34. Luisada, A. Treatment of paroxysmal pulmonary edema: with special reference to forms occurring under wartime conditions. *Exper. Med. & Surg.* **1**:22-30, 1943.
35. Eason, E., and Karp, M. Acute pulmonary edema. *Anesthesiology* **4**: 508-515, 1943.
36. Bookhamer, J. W., and Cullen, S. C. Pulmonary edema during anesthesia — case reports. *Anesthesiology* **4**:263-265, 1943.
37. Keser, V. L'oedème pulmonaire aigu d'origine centrale. *Rev. méd. de la Suisse Rom.* **62**:38-47, 1942.
38. Vidal, J., Fourcade, J., and Girard, M. Réaction contro-latérale d'oedème aigu pulmonaire provoquée par la création d'un pneumothorax extra-pleural. *Presse méd.* **51**:37, 1943.
39. Weisman, S. J. Edema and congestion of lungs resulting from intracranial hemorrhage. *Surgery* **6**:722-729, 1939.
40. Weber, F. P., and Blum, K. Acute pulmonary oedema with hypoglycemic coma: example of acute pulmonary oedema of nervous origin. *J. Neurol. & Psychiat.* **5**:37-39, 1942.
41. Nielsen, J. M., Ingham, S. D., and von Hagen, K. O. Pulmonary edema and embolism as complications of insulin shock in treatment of schizophrenia. *J. A. M. A.* **111**:2455-2458, 1938.
42. Dubel, G. Oedèmes aigus du poumon d'origine nerveuse. 27 pp. Paris thèse, 1939.
43. Tardieu, M. Sur le traitement de l'oedème aigu pulmonaire d'origine nerveuse. *Presse méd.* **51**:232, 1943.
44. Trillot, M. Fracture du crâne avec hémorragie extra-durale: mort rapide par oedème aigu du poumon. *Presse méd.* **51**:280, 1943.
45. Delannoy, E., and Muller, M. Plaie sèche de la carotide externe par coup de feu. *Ann. de méd. lég.* **14**:860-863, 1934.
46. Broutin. Étude sur le rôle du système nerveux dans l'oedème aigu du poumon. 40 pp. Paris thèse, 1939.
47. Grace, E. J., and Linnehan, E. H. Fatalities in phrenic nerve surgery. *Surg.* **32**:105-107, 1936.
48. Papafotis, C. De la part jouée dans la pathogenie d'oedème aigu du poumon par les troubles vago-sympathiques. 51 pp. Paris thèse, 1930.
49. Shanahan, W. T. Acute pulmonary oedema as complication of epileptic seizures. *New York M. J.* **87**:54-56, 1908.
50. Ohlmacher, A. P. Acute pulmonary oedema as terminal event in certain forms of epilepsy. *Am. J. M. Sc.* **139**:417-422, 1910.
51. Langeron, L. L'oedème aigu du poumon — manifestation viscerale de l'epilepsie. *Presse méd.* **33**:65-67, 1925.
52. Riesman, D. Acute pulmonary oedema with special reference to recurrent form. *Am. J. M. Sc.* **133**:88-100, 1907.
53. Newmyer, S. W. Acute idiopathic pulmonary oedema. *New York M. J.* **86**:925, 1907.
54. Freedberg, A. S., and Altschule, M. D. Effects of infection on circulation. *New Eng. J. Med.* **233**:560-567, 1945.
55. Bard, L. Nature et mécanisme pathogenique de l'oedème aigu du poumon. *Presse méd.* **34**:1489-1491, 1926.
56. Gibbon, J. H., Jr., and Gibbon, M. H. Experimental pulmonary edema following lobectomy and plasma infusion. *Surgery* **12**:694-704, 1942.

57. Donzelot, E., and Ménétrel, B. L'infiltration stellaire dans le traitement des crises récidivantes d'oedème aigu pulmonaire. *Bull. et mém. Soc. méd. d'hôp. de Paris* **56**:679-681, 1940.
58. Fisher, A. J. Pulmonary edema as complication of spinal anesthesia. *Anesthesiology* **4**:640, 1943.
59. MacKenzie, J. B., and MacKenzie, C. G. Production of pulmonary edema by thiourea in rat. *Proc. Soc. Exper. Biol. & Med.* **54**:34-37, 1943.
60. Choisy, R. Oedème pulmonaire d'origine neuro-hormonale? *Rev. méd. de la Suisse Rom.* **60**:1067-1082, 1940.
61. De Burgh Daly, I. Reactions of pulmonary and bronchial blood vessels. *Physiol. Rev.* **13**:149-184, 1933.
62. Olkon, D. M., and Joannides, M. Capillary circulation in alveolus pulmonalis of living dog. *Arch. Int. Med.* **45**:201-205, 1930.
63. De Burgh Daly, I., and von Euler, V. Functional activity of vasomotor nerves to lungs in dog. *Proc. Roy. Soc., London, s. B.* **110**: 92-111, 1932.
64. Franklin, K. J. Actions of adrenalin and of acetyl-choline on isolated pulmonary vessels and azygos vein of dog. *J. Physiol.* **75**:471-479, 1932.
65. Berry and De Burgh Daly. Cited by De Burgh Daly.[61]
66. Kuré, K., Ikeda, R., and Sakurasama, F. Spinal parasympathetic. X. Vasoconstrictor effect of spinal parasympathetic on pulmonary vessels. *Quart. J. Exper. Physiol.* **22**:339-360, 1933.
67. Heidenhain and Klemensieviez. Cited by Luisada.[27]
68. Miller, W. S. *The Lung*. 209 pp. Springfield: Charles C Thomas, 1937.
69. Karsner, H. T. Nerve fibrillae in pulmonary artery of dog. *J. Exper. Med.* **14**:322-325, 1911.
70. Larsell, O., and Dow, R. S. Innervation of human lung. *Am. J. Anat.* **52**:125-146, 1933.
71. Ponzio. Cited by Gaylor, J. B. Intrinsic nervous mechanism of human lung. *Brain* **57**:145-160, 1934.
72. Rasmussen, A. T. Pathways for nervous reflexes from parenchyma of lung. *Am. Rev. Tuberc.* **13**:545-549, 1926.
73. Farber, S. Neuropathic pulmonary edema: further observations. *Arch. Path.* **30**:180-197, 1940.

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CASE 32421

PRESENTATION OF CASE

A seventy-eight-year-old retired electrician entered the hospital because of swelling of the legs.

Ten months before admission the patient first began to have cramps in the right calf on walking short distances. Soon pains occurred in both legs, increasing in frequency and intensity until four or five months before admission, when they were more or less constant throughout each day. Occasionally the cramps also occurred at night during sleep. Three weeks before admission attacks of nocturnal dyspnea occurred at least once and later three or four times nightly. Associated with the attacks was a slight nonproductive cough. There had been no exertional dyspnea or anginal pain. There had previously been no history suggestive of cardiac difficulty. The patient had slept on two pillows for many years.

Two and a half weeks before admission swelling of the ankles and legs appeared for the first time. The legs were cool and red. Numerous small purple spots developed over the dorsums of both feet and the medial aspects of the calves. The swelling increased rapidly. Two weeks before admission spontaneous drainage of watery fluid from both legs began. The swelling extended slightly above the knee. There was no history of hypertension, headaches, tinnitus or visual disturbances.

Physical examination showed the patient to be moderately orthopneic. The neck veins just above the clavicle were engorged and pulsating in the upright position. The heart was enlarged, the border being 12 cm. left of the midsternal line in the fifth interspace. The rhythm was irregular, and the rate was 120, with a pulse deficit of 20. No murmurs were heard. There were bilateral fine basal rales and decreased breath sounds, voice sounds and tactile fremitus. The liver edge extended 3 cm. below the rib margin. Below the knees there was ++++ pitting edema. The skin was tense, red, cool and dripping with moisture. There were purpuric spots and telangiectasis on the medial aspects of both thighs. No arterial pulsations were felt below the femoral vessels. The legs were not tender.

The temperature was 98°F., and the respirations were 20; the blood pressure was 160 systolic, 90 diastolic.

Examination of the blood showed 16 gm. of hemoglobin and a white-cell count of 10,000, with 86 per cent neutrophils. A chest film showed moderate bilateral pleural fluid, widened pulmonary vessels and predominantly right-sided cardiac enlargement (Fig. 1). An electrocardiogram was interpreted as showing auricular fibrillation, and enlargement and strain of the left side of the heart, without significant coronary disease. The circulation time (Decholin) was 29 seconds (normal, 12 to 18 seconds).

With bed rest and Purodigin the patient's condition improved rapidly, the rales disappeared and the swelling of the legs diminished markedly. The pulse remained irregular at 80 per minute. At 8:30 p.m. on the fifth hospital day mild, cramping, nonradiating pain suddenly developed in the lower abdomen. There was no nausea or vomiting. Six loose nonbloody bowel movements were passed with moderate but incomplete relief in the first hour after the onset of the abdominal pain. The abdomen was soft and nontender. Peristalsis was normally active, and there was no rebound tenderness. Rectal examination was negative. A stool specimen was guaiac negative. There was no liver or costovertebral-angle tenderness. The liver and spleen could not be felt. The lungs were clear. The blood pressure was 150 systolic, 90 diastolic; the pulse was 160 and regular. The temperature was 98° F. The white-cell count was 16,000, with 90 per cent neutrophils. A cardiette examination showed auricular flutter, with a 2:1 block. Six milligrams of morphine

and quinidine was given. There was little change during the night except for progressive apprehension and beginning disorientation. On the sixth hospital day, eleven hours after the onset of the attack, the patient was much worse, and could be roused only with difficulty. The temperature was 100.5°F., the pulse had dropped to 65, the respirations had risen to 40 and the blood pressure had dropped to 90 systolic, 40 diastolic. The white-cell count climbed to 26,000. The abdomen was markedly distended and moderately tender in both lower quadrants. There were no masses or rebound tenderness. Peristalsis was absent. No urine was passed. Twenty hours after the onset of the attack the patient was moribund and in deep shock, with a cold moist skin, an imperceptible blood pressure and Cheyne-Stokes respirations. He stopped breathing twenty-seven hours after the onset of the attack.

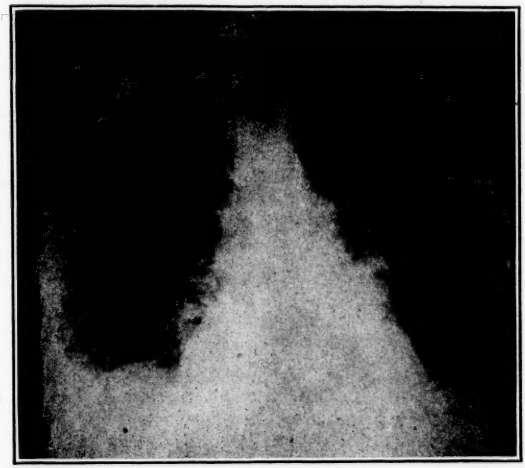

FIGURE 1.

DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH: This case starts with a typical history of peripheral arteriosclerosis involving the legs. The swelling of the ankles and legs at a later time raises the question of whether the patient developed cardiac decompensation or whether he had a superimposed attack of venous thrombosis.

"Two weeks before admission spontaneous drainage of watery fluid from both legs began." This implies the diagnosis of cardiac decompensation with edema, because such an occurrence with primary thrombophlebitis is extremely rare.

The hemoglobin was slightly high and raises the question of polycythemia, but I assume that it was merely due to the accentuation of cardiac difficulties, with a certain amount of dehydration, and had no further significance. The prothrombin time was also elevated, but I doubt if it was important from the point of view of the final diagnosis.

Up to this point the case has been more or less a routine problem, and we are then presented with the final episode. At the time of this episode, I assume that the resident in charge of the medical wards thought that the patient was probably suffering from acute enteritis, and although a complete and careful physical examination was indicated there did not seem to be any tremendous urgency about the case until the following morning. May I point out that if an examination is made immediately after the onset of an intra-abdominal surgical emergency, it may be almost negative and quite misleading. In other words, it takes a few hours for enough signs to develop to make a diagnosis. Hence, a great difference may be noted in the abdomen three hours after the onset of the illness or at the most six hours afterward. In the case under discussion there were progressive apprehension and beginning disorientation during the night. In the morning the patient was obviously a sick man and dying rather rapidly. At that time there was no indication for surgical help; the patient would merely have been speeded on his way.

The differential diagnosis, then, reduces itself to the question, What abdominal catastrophe could produce death in this short period of twenty-seven hours? There are only a few things that need be discussed: mesenteric thrombosis, acute pancreatitis, dissecting aneurysm and volvulus. Several of them can be disposed of easily. In the first place, pancreatitis, which can rapidly produce shock and death, can be ruled out because there was no vomiting, all the symptoms were referable to the lower abdomen, and there was no tenderness at any time over the pancreas.

Dissecting aneurysm or some lesion of that type within the abdominal cavity can produce rapid death. Again, the history is unusual for that. The pain usually starts in the chest but later shifts to the abdomen. It would be of interest if we had had a report on the condition of the femoral vessels during the later examinations because if there is a dissecting aneurysm frequently one or both vessels become obliterated as time goes on. Again, with this diagnosis, pain should be steady.

Volvulus of the bowel could conceivably produce death in this short time, but it is unlikely. This would have been the first attack of volvulus — a rare occurrence in a man of seventy-eight. Usually there are repeated attacks before a fatal attack occurs.

By far the most attractive diagnosis is that of mesenteric thrombosis. There is nothing incompatible with that diagnosis. In the first place, the pain came on suddenly and was crampy. Crampy pain is not at all infrequent with mesenteric thrombosis, although the pain is often steady. The diarrhea is suggestive of involvement of the bowel. The physical findings at the onset are often as negative as they were in this case. I might mention that normal peristalsis is a misleading sign. Most of you know that again and again there can be acute inflammation or a vascular lesion in the abdomen with normal peristalsis. In the case under discussion, as time went on, shock developed, the white-cell count rose to 26,000 and evidence of peritoneal irritation appeared. All these signs are typical of mesenteric thrombosis. The fact that no urine was passed can indicate one or two things — either complete block of the renal artery by thrombosis, which is extremely unlikely with mesenteric thrombosis, or, much more probably, that the patient was in a state of shock.

If this was mesenteric thrombosis, what type was it? Could the patient have had an arterial embolus, or was it primary arterial or venous thrombosis? It is a difficult differential diagnosis to make. I might merely say that if venous thrombosis occurs as the primary incident, the symptoms are likely to last for several days before the case is considered a surgical emergency. On the other hand, if the obstruction is arterial in type, it is much more probable that the patient will either die or come to operation rapidly. I doubt if this was an arterial embolus because the pulse was still irregular and the patient was still fibrillating at the time the pain started. If he had stopped fibrillating or had had other cardiac changes at that time, an embolus would be likelier. I think that this patient died of mesenteric thrombosis that was primary in the arterial system but at the time of autopsy involved both mesenteric arteries and veins.

DR. TRACY B. MALLORY: Do you want to see the x-ray films?

DR. WELCH: I did not know that there were any.

DR. MILFORD D. SCHULZ: I do not believe that they contribute anything.

DR. WELCH: They might be of interest, but I shall not change the diagnosis.

DR. ALLAN M. BUTLER: What would you have done on the ward? Would you have liked a plain film of the abdomen when the pain started?

DR. WELCH: Later on.

There is an x-ray picture described as being typical of mesenteric thrombosis. The scout film looks like intestinal obstruction running over to the splenic flexure. When a barium enema is given, however, no evidence of obstruction is found.

DR. SCHULZ: The film shows enlargement of the heart, engorgement of the hilar vessels, particularly on the left, and fluid in the pleural sinuses.

DR. LEWIS K. DAHL: I should like to ask Dr. Welch what he would have done if he had been on the ward and made the diagnosis of mesenteric thrombosis.

DR. WELCH: That is a difficult question to answer. In the first place, the man was seventy-eight years old and had to die sometime. I think that the surgeon must seriously consider whether postponing death is necessarily desirable or even justified. We know that this man was old and that in such cases the operative mortality for mesenteric thrombosis is 90 per cent. But being a surgeon I should probably have advised operation, realizing that it would probably have killed him but might possibly have saved him temporarily.

CLINICAL DIAGNOSES

Arteriosclerotic heart disease.

Cardiac failure.

Mesenteric thrombosis.

DR. WELCH'S DIAGNOSIS

Mesenteric thrombosis, arterial and venous.

ANATOMICAL DIAGNOSES

Embolism, superior mesenteric artery.

Arteriosclerosis, generalized, severe.

Arteriosclerotic aneurysm of thoracic aorta, with mural thrombosis.

Hypertrophy of heart.

Pathological Discussion

Dr. Mallory: The immediate cause of death in this case was occlusion of the mesenteric artery. It was not due to local thrombosis, however, but to an embolus. The source of the embolus was not in the heart. It was a large fusiform arteriosclerotic aneurysm of the thoracic aorta. I was hoping that Dr. Schulz would show that to us.

Dr. Schulz: What I took to be part of the left lung root is the aneurysm.

Dr. Mallory: The aneurysm measured 13 cm. in length. It was partially filled with an adherent long-standing clot. The clot found in the superior mesenteric artery was of the same color and consistence as that in the aorta and was not adherent as it would have been if formed locally; I therefore think that we can be reasonably sure that it was an embolus. The other findings were not of any particular significance. There was widespread generalized arteriosclerosis; the heart was slightly hypertrophied, and the majority of the other organs showed only senile atrophy, which would be expected at the age of seventy-eight.

CASE 32422

Presentation of Case

A sixty-six-year-old watchman entered the hospital because of painless hematuria.

The patient had his first attack of hematuria three months before entry, when he was taking sulfonamides for an upper respiratory infection. The attack lasted for four days. The patient then remained asymptomatic until three weeks before entry, when he had another entirely spontaneous episode lasting one day during which he passed grossly bloody urine and clots; there was no pain with the bleeding. He was seen at that time in the Out Patient Department, where cystoscopy showed the blood to be coming from the right ureter. An intravenous pyelogram revealed a reduplication of the right urinary passage, with the point of reduplication not demonstrable. One ureter led into the middle and lower calyxes, and the other led to the upper calyx. The minor calyxes, particularly the lower, were incompletely visualized, and there was a questionable filling defect. The urinary passages on the left side were normal. There was an irregular, filling defect along the floor of the bladder over the region of the prostate, and at least one small diverticulum on the left side of the bladder. The patient had had no other urinary symptoms and passed a good stream. He had had no chills or fever and had recently gained 4 pounds.

Seven years before entry the patient was in another hospital because of a "cavity in the right lower lobe." Healing was apparently spontaneous, and he was discharged in three weeks. During the following six years he suffered from pain in the right chest whenever he caught cold. He was seen in the Medical Out Patient Department six months before admission, when a chest x-ray film showed increased density in the region of the right apex and first interspace that was interpreted as probably inactive tuberculosis.

Physical examination was negative except for a boggy, nontender prostate, enlarged to about twice the normal size.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 4,450,000, with 80 per cent hemoglobin, and a white-cell count of 9700. The nonprotein nitrogen was 30 mg. and the total protein 6.4 gm. per 100 cc., and the chloride 101 milliequiv. per liter. The prothrombin time was normal. The urine was light amber and acid, and had a specific gravity of 1.012; it gave a ++ test for albumin, and the sediment contained 20 red cells and 4 white cells per high-power field. A culture and smear were sterile.

An x-ray film of the chest showed no change from the previous examination. A retrograde pyelogram revealed the reduplication on the right to be complete. The lowermost group of calyxes were not unusual. In the upper group a filling defect was again seen, and there were two rounded areas measuring about 1.5 cm. in diameter each, consistent with nonopaque stones or tumor (Fig. 1). A plain film over the region of the right kidney showed minimal flecks of calcification in the region of the upper pole in, and corresponding to, the location of the mass seen in the pyelogram.

An operation was performed.

Differential Diagnosis

Dr. Wyland F. Leadbetter: I do not know how much sulfonamide this patient was taking or whether he was taking sodium bicarbonate with it. There is a possibility that this therapy had a bearing on the subsequent events, but it is unlikely.

Painless hematuria in the presence of clots, particularly large clots, might be thought to be due to bleeding from the bladder, because bleeding from the kidneys, if massive and with clots in the renal pelvis, is quite apt to produce renal colic. That statement, however, ought not to be taken as a definite rule — simply something to bear in mind.

It is impossible to make a definite diagnosis from the intravenous urograms. The record simply states that the urinary passages on the left were normal. Therefore, we can say that this patient presumably had hematuria coming from the right upper urinary tract, but we do not know whether it came from the upper or lower half of the right kidney.

At cystoscopy there was no mention of a tumor of the bladder. The irregular filling defect, I sup-

pose, was visualized from the cystogram. The fact that there was a diverticulum suggests that there was or had been some obstruction to the lower urinary passage.

The lung cavitation is interesting. It seems unlikely that that was a tuberculous infection. It was possibly a lung abscess that healed. I can not see that it had any bearing on the present situation.

White cells in the urine could be associated with the bleeding and need not be an indication of infection.

The retrograde pyelogram should be the key to the diagnosis in this case, and we might see the films now.

DR. MILFORD D. SCHULZ: This is a representative film, and the left side appears to be normal.

FIGURE 1.

An x-ray film taken six months before admission showed inactive tuberculosis of the right upper lobe. That might have had a bearing on the present illness, but I do not believe that we can do much more than assume that this patient had had active pulmonary tuberculosis at one time.

The lower calyxes and ureter on the right seem also to be quite normal, but there is something amiss in the calyx of the upper half. In the reduplicated right kidney there is a round, lobulated, filling defect that is better seen on the retrograde film.

DR. LEADBETTER: Is there any calcification in that area?

DR. SCHULZ: There is no calcification in that area, and the ureter leading to the involved calyx is normal.

DR. ALLAN M. BUTLER: There is no calcification, but does that rule out a stone?

DR. SCHULZ: No; nor does it rule out tuberculosis.

DR. BUTLER: Is the incompleteness of the filling of the right upper half a possible indication of a stone that is not radio-opaque?

DR. SCHULZ: It could be a nonopaque stone, blood clot, tumor or granulation tissue — anything that displaces the opaque material in the pelves and calyxes.

DR. LEADBETTER: May we see the film that outlines the ureter?

DR. SCHULZ: There is nothing remarkable about it, except that it shows the upper third of the ureter, which looks perfectly normal. There is a film showing a little more of the lower ureter on that side, but there is nothing of further interest.

DR. LEADBETTER: Will you be willing to comment on the cystogram?

DR. SCHULZ: The irregularity in the floor of the bladder looks as if it might be due to prostatic enlargement. The diverticulum is probably associated with the irregularities and trabeculations seen throughout the wall of the bladder.

DR. LEADBETTER: This illustrates the point that when hematuria is present it is necessary to work the case up completely to determine accurately the site of bleeding and to obtain good pyelograms, if the upper urinary tract is involved. The history in this case was one of short duration, with two episodes of gross hematuria, and I think that we can definitely say that the bleeding came from the right urinary tract. In view of the finding in the upper half of the right kidney, we must assume that the bleeding originated there, although there is no direct statement to that effect. We may assume that there was benign prostatic hyperplasia, which accounts for the changes and the irregularities in the bladder floor and the diverticulum of the bladder.

What was the lesion in the upper pole of the right kidney? The x-ray studies show a definite filling defect, although it is not clearly outlined. The diagnosis seems to rest between tumor, tuberculosis and nonopaque calculi. There is one other point to be noted regarding the filling defect: it does not appear to be free in the pelvis. Whatever the lesion was, it was associated with calyxes or with the parenchyma and was not free in the true pelvis. For that reason I should be inclined to rule out the possibility of nonopaque stone. If we were more critical about this pyelogram we could say that this shadow represents the upper calyx, and these, the lower and midcalyxes in the upper portion of the kidney. There appears to be dye extending up about the filling defect and possibly representing infiltration of dye into the kidney substance. This is somewhat suggestive of renal tuberculosis. On the other hand, we are dealing with an illness of short duration and the ureter appears normal. In renal tuberculosis the ureter usually shows characteristic changes, and I am inclined to think that one is obligated to make a diagnosis of renal tumor.

DR. BENJAMIN CASTLEMAN: Would the shadow be round if it were due to tuberculosis?

DR. LEADBETTER: Not usually, but I think one can find almost anything in a cavitation due to tuberculosis. On the basis of the history and the x-ray findings I believe that one must make a diagnosis of tumor involving the upper pole of the kidney. It is necessary to differentiate papillary tumor of the pelvis and renal-cell carcinoma — that is, a tumor originating in the renal parenchyma. It is difficult to decide in this case. The outline of the kidney is not definite in the films, but it is fairly obvious that there is no enlargement of the upper pole of the kidney, and it is probably better to make a diagnosis of papillary carcinoma of the renal pelvis, involving the upper half of the right kidney, benign prostatic hyperplasia and, in addition, inactive tuberculosis of the right upper lobe of the lung.

DR. JAMES B. TOWNSEND: How often will tuberculosis reveal itself as painless hematuria?

DR. LEADBETTER: Quite often; it is one of the most frequent signs of early renal tuberculosis. On the basis of the pyelogram showing the essentially normal ureter it is difficult to make a diagnosis of renal tuberculosis.

DR. TOWNSEND: I suppose that efforts were made to do guinea-pig inoculation.

DR. CASTLEMAN: I do not believe that they waited that long.

DR. BUTLER: This summary does not tell anything about what was found in the urine by ureteral catheters at the retrograde cystoscopic examination. With catheters up the two ureters on the side where disease was suspected and with catheters up the ureter on the side where no disease was suspected, one had a wonderful opportunity to see what kind of urine was coming from each portion of the kidney. Was any such information obtained?

DR. CASTLEMAN: Yes; the material was both cultured and injected into a guinea pig.

Clinical Diagnosis

Tumor, upper pole of right kidney.

Dr. Leadbetter's Diagnoses

Papillary tumor, right kidney pelvis, involving upper half of double pelvis.
Benign prostatic hyperplasia.

Anatomical Diagnosis

Papillary carcinoma (Grade II A), involving upper half of bifid pelvis.

Pathological Discussion

Dr. Castleman: At operation the lesion proved to be a papillary carcinoma, which was graded as II A. As Dr. Leadbetter predicted, it was attached to the pelvis and extended into the calyx for a short distance. The ureter was removed at the same time because papillary tumor was suspected. The patient made an uneventful convalescence and was seen a month or two later.

Dr. Leadbetter: Was the whole kidney removed?

Dr. Castleman: The entire kidney was removed; the lower calyxes showed petechial hemorrhage — I assume from operative trauma. There was nothing in the lower half.

Dr. Leadbetter: I think it would be possible to remove only the upper half if one could be sure of the diagnosis, and I think that if one could visualize the pelvis it might be possible to make the diagnosis.

Dr. B. T. Towery: Were there any ureteral implants?

Dr. Castleman: No.

Dr. Butler: Would it not have been an advantage to take a lateral film at the time of either the intravenous or retrograde pyelograms?

Dr. Schulz: I do not know about this case, but lateral films taken at the time of retrograde pyelography are often helpful, especially in the demonstration of tumor.

Dr. Butler: That is why I thought that when the possibility of tumor is suspected it would be justified.

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SALVATION ARMY LOOKS AHEAD

The Salvation Army was founded in London in 1864 by William Booth to carry out "the fundamental purpose of taking the Gospel to those who need it but will not seek it." After eighty-two years this evangelistic organization, functioning as the world's greatest system of social services, carries on its work and has its headquarters in every country on the face of the globe. It is infinite in its capacity for mercy; its doors are closed to no one; it works in its own centers and in its hospitals; it finds room for its services in the home and in the street, in the church and in the prison cell.

This month the Salvation Army of Greater Boston is asking for a million dollars. The sum is greater than its usual request because, in addition to its customary and postwar services, it must have $149,000 for remodeling of five corps centers and $375,000 for a new Evangeline Booth Home and Hospital.

The Evangeline Booth Home and Hospital of Boston, one of thirty-five similar institutions operated by the Salvation Army in this country, was opened as a home in Dorchester in 1892. In 1900 it moved to larger quarters, and the hospital department was established; twenty years later, when it entered its present quarters on West Newton Street, the hospital department was separated from the home department and reorganized as a regular maternity hospital equipped to receive patients of the medical staff.

The home cares for unwed mothers regardless of multiparity; the hospital, in which 764 babies were delivered in 1945, is an obstetric teaching unit of Tufts College Medical School, approved by the American Medical Association and the American College of Surgeons. It also conducts a training school for attendant nurses. During the war the hospital was made available to medical personnel of the United States Coast Guard for the delivery of Coast Guard wives.

A general improvement in hospital standards combined with a desire to give increased and better service has forced the Evangeline Booth Home and Hospital to the decision to abandon its present inadequate quarters. It now needs a lying-in hospital of eighty to a hundred beds, with a separate building for the home department, and is asking the public to provide funds to fill this need, even in a year when larger hospitals are experiencing growing pains and are expressing their own needs for expansion. It may be taken for granted that the people of Greater Boston, among their other commitments, will continue to support this essential charity.

RADIOACTIVE IODINE IN THE TREATMENT OF THYROTOXICOSIS

Among the recent significant contributions of physics to medicine are studies with radioactive iodine. Dr. Saul Hertz, working in collaboration with Drs. Arthur Roberts, Robley Evans, William Salter and others, utilized this isotope in studying some fundamental mechanisms of function of the thyroid gland, especially those concerned with

iodine metabolism. In 1942, Hertz and Roberts,[1] and also Hamilton and Lawrence,[2] rendered preliminary reports of the effects of therapy with radioactive iodine in the treatment of thyrotoxicosis. The results encouraged an extension of the studies by Hertz and Roberts.[3] On the basis of these observations, Chapman and Evans[4] were prompted to use larger doses of radioactive iodine than previously had been used in thyrotoxic patients.

The basis for such therapy arises from the fact that, since in untreated hyperthyroidism the thyroid gland can take up as much as 80 per cent of a small dose (less than 2 mg.) of iodide within a few hours after its administration, it is possible to obtain concentrated irradiation at the site desired without undue exposure of other tissues. Although the total number of patients treated with radioactive iodine is relatively small, the results of this type of treatment appear encouraging. Hertz and Roberts[3] report that, in 29 uniodinized patients with hyperthyroidism whose goiters weighed from 60 to 75 gm., radioactive iodine in doses of 5 to 25 millicuries cured the disease in about 80 per cent. Chapman and Evans[4] observed that, in 22 patients with hyperthyroidism whom they treated with larger amounts (14 to 52 millicuries) of radioactive iodine, 14 responded well to the single dose. Three were given two doses, and 5 were given three doses, and as a rule, the subsequent doses were larger than the first one. Four patients later developed myxedema, and 2 had a persistence of thyrotoxicosis following treatment, although the disease became less intense.

The chief problem in the use of radioactive iodine is to determine the optimal dose. The amount required depends on the amount of iodine in the body, the size of the thyroid gland, the nature of the pathologic changes in the gland and many other conditions. Inability to estimate these factors accurately makes it more difficult to select the proper dose than it is for the surgeon to decide how much of the thyroid tissue should be removed. In either instance, only a slight difference in the number of cells that are permitted to live may result in a persistence of the thyrotoxicosis or the development of myxedema. It appears wise to use a minimal dose of radioactive iodine, since additional doses can be given if needed; with excessive therapy some patients may develop permanent myxedema. Few other ill effects from the use of radioactive iodine therapy have been observed. Occasional patients have had transient reactions resembling roentgen-ray sickness. Whether this type of treatment predisposes to the development of cancer or whether structural damages will subsequently occur in other tissues remains to be ascertained.

The extent of usefulness of this form of therapy has not been determined. In certain complicated cases it is unquestionably the treatment of choice. Moreover, it appears to be useful in some patients who have been unsuccessfully treated with thiouracils and in those who have not obtained good results after having been subjected to surgical treatment. Indeed, it is possible that this form of therapy may become the one of choice in the majority of patients with thyrotoxicosis, but this can be established only on the basis of the findings in extended investigative studies.

References

1. Hertz, S., and Roberts, A. Application of radioactive iodine in therapy of Graves' disease. *J. Clin. Investigation* **21**:624, 1942.
2. Hamilton, J. G., and Lawrence, J. H. Recent clinical developments in therapeutic application of radio-phosphorus and radio-iodine. *J. Clin. Investigation* **21**:624, 1942.
3. Hertz, S., and Roberts, A. Radioactive iodine in study of thyroid physiology. *J. A. M. A.* **131**:81-86, 1946.
4. Chapman, E. M., and Evans, R. D. Radioactive iodine in hyperthyroidism. *J. A. M. A.* **131**:86-92, 1946.

NOTICES

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, October 23, in Boston.

PROGRAM

12:00 m. Clinicopathological Conference of the Children's Hospital (held temporarily at the Peter Bent Brigham Hospital Amphitheater). Members of the Society are invited to attend.

1:15 p.m. Luncheon at Vanderbilt Hall, Harvard Medical School (price, 70 cents).

2:00 p.m. Regular Combined Clinic. Main Amphitheater, Children's Hospital.

3:00 p.m. Presentation of patients with tumors. Main Amphitheater, Children's Hospital. Members of the medical profession and students are invited to attend.

5:30 p.m. Refreshments at Longwood Towers.

6:30 p.m. Dinner at Longwood Towers (price, $2.50, including tax). Members of the Society and their guests are invited to attend.

7:30 p.m. Tumors in Infants and Children. Children's Hospital. Dr. Sidney Farber. Members of the medical profession and students are invited to attend.

NEW ENGLAND ROENTGEN RAY SOCIETY

The New England Roentgen Ray Society will hold its first meeting of the season on Friday, October 18, at the Hotel Beaconsfield, Brookline, Massachusetts. At 4:30 p.m. there will be an x-ray conference on diseases of the gastrointestinal tract. At 8:00 p.m. Dr. Frederic E. Templeton, of Seattle, Washington, will speak on "The Esophagus — Some Roentgenologic Observations on the Muscular Action in the Normal and Abnormal." Interested physicians are invited to attend.

(*Notices continued on page xiii*)